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Alterations in Numbers of Circulating Platelets Following Surgical Operation and Administration of Adrenocorticotropic Hormone

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The factors influencing alterations in circulating platelets following surgical operations are analyzed. There is probably no bone marrow depression following surgery which might be responsible for the early thrombocytopenia, nor is operative hemorrhage sufficient to do so. Evidence procured from administration of adrenocorticotropic hormone suggests that adrenal hyperactivity, a result of the stress of operation, may play an important part in the early postoperative thrombocytopenia. The later thrombocytosis was, however, not observed following administration of this drug.

NUMEROUS studies on postoperative venous thrombosis indicate that it may be in part due to alterations in the coagulation mechanism induced by the operation rather than entirely to the more commonly incriminated factors of venous stasis or roughened endothelium. Of the coagulation factors affected by a surgical operation the platelets have shown the most consistent changes.[1] A thrombocytopenia during the first three or four postoperative days followed by a thrombocytosis during the second postoperative week is the characteristic response to a major operation of the magnitude of partial gastrectomy or pulmonary resection. What part, if any, this platelet tide plays in causing postoperative thrombosis is not kown. It is possible, however, that examination of the factors influencing it would point the way to more rational prophylaxis against postoperative thrombosis.

A fall in circulating platelets could be caused by decreased platelet production or by "peripheral" loss. A study by Kerhulas and co-workers[2] of the activity of megakaryocytes in the bone marrow failed to show valid evidence of depression of activity three days after operations. Further work performed in this laboratory has shown no alteration in platelet adhesiveness during that part of the postoperative period (fig. 1). Since Wright[3] has produced evidence which suggests that increased adhesiveness of platelets is indicative of platelet regeneration, this serves as further testimony against a change in bone marrow activity as the cause of the early thrombocytopenia. In further attempts to explain it we have, therefore, directed our attention to a search for possible causes of peripheral platelet losses. Observations on two of them, hemorrhage and the endocrine response of the body to stress, are reported in this communication.

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METHODS

Platelet Counts. Venous blood was used and diluted with the sucrose, citrate, cresyl blue solu-

tion* modified by Pohle[5] after Reese and Ecker.[6] Where syringes were used, it was drawn by clean venipuncture through chemically clean needles into chemically clean dry syringes. In the experiments on hemorrhage the blood was allowed to drip from the needle onto a glass slide whence it was immediately aspirated into the pipet and diluted. In the experiments in which the effect of corticotropin (ACTH) was compared with that of operation the blood was oxalated, using 0.5 cc. of a solution containing 2 Gm. of potassium oxalate and 3 Gm. of ammonium oxalate in 500 cc. of distilled water. This 0.5 cc. was allowed to dry in an oven so that each oxalate bottle which was to receive 4.5 cc. of blood contained 0.0002 Gm. of potassium oxalate and 0.0003

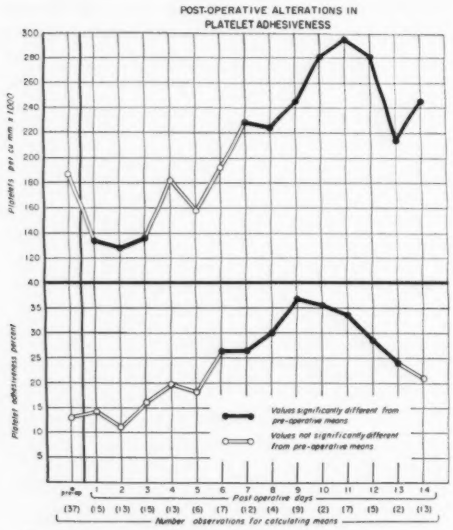

FIG. 1.—Platelet adhesiveness determined according to the method of H. P. Wright.[4]

Gm. of ammonium oxalate. The blood was drawn to the 0.5 mark of a red cell pipet which was then immediately filled with platelet diluting fluid to the 101 mark making a dilution of 1 to 200. In the case of the oxalated blood the dilution into the pipet was made within one hour after the blood was drawn. The pipets were then shaken for from one to three minutes, some of the mixture discarded and the counting chambers of a standard hemocytometer filled with the mixture. The platelets were allowed to settle for 15 minutes in a humid atmosphere, one compartment 1 mm. square and 0.1 mm. deep was then counted and the result multiplied by 2000 to procure the number of platelets per cubic millimeter of blood.

* The diluting fluid consists of sucrose 20 Gm., sodium citrate 5 Gm., brilliant cresyl blue 0.1 Gm., dissolved in 250 cc. of distilled water.

Multiple counts performed as unknowns on the same normal individual from day to day and on the same blood sample have consistently shown a standard deviation of not greater than 20,000 platelets, a coefficient of variation of not greater than 10 per cent.

Eosinophil Counts. The method of Hunneman and associates[8] was used. Venous blood oxalated in the manner described above was drawn into the standard white cell counting pipet to the 1 mark and diluted up to the 11 mark making a 1:10 dilution with a fluid consisting of 0.1 per cent phloxine and propylene glycol mixed in equal volumes with distilled water, as described by Roche, Hills and Thorn[7] and Hunneman, Wexler and Westenhaver.[8] After allowing 15 minute for staining, the pipets were shaken for from one to three minutes and both counting chambers of a hemocytometer were filled. The fluid was allowed to settle for 15 minutes in a humid atmosphere and counts were then performed. By counting the eosinophils in eight of the 1 mm.^{2} segments and multiplying the result by 12.5 the eosinophils per cubic millimeter of blood were found.

The patients studied were individuals undergoing operations of the magnitude of a subtotal gastrectomy or lobectomy none of which lasted longer than four hours nor less than two and in none of which less than one blood transfusion nor more than four were administered. The normal individuals studied were members of the professional staff, laboratory personnel or volunteer patients who were suffering from no active physical disease, such as those convalescing from fractures incurred at least two months before.

OBSERVATIONS

Effect of Hemorrhage on Platelets

In 11 patients undergoing surgical operation platelet counts were performed immediately before the induction of anesthesia and within 30 minutes after the termination of the operation. Platelet counts were also performed on the blood used for transfusion, the amount of transfused blood being recorded. The amount of blood lost was determined by the method of weighing sponges.[10] By comparing the platelet counts before and after operation and arbitrarily setting the blood volume at 6000 cc., a rough estimate was derived of the total number of platelets which actually disappeared from the circulation. By assuming that the blood shed during the operation contained platelets in concentrations indicated by the preoperative platelet count the numbers of platelets lost due to hemorrhage were estimated and from these were subtracted those

replaced by transfusion. Table 1 indicates the results of the observations and demonstrates that there is a large disparity between the small numbers of platelets of the shed blood and the large numbers which disappeared from the circulation during operation. Actually, as will be shown below, the platelet counts of the blood shed during operation must have been considerably lower than that of the pre-

TABLE 1.—*Platelet Losses at Operation*

Case	Estimated Change in Total Platelets from Hemorrhage & Transfusion—Billions	Estimated Change in Total Platelets from Platelet Counts—Billions
1	−11	−372
2	+96.5	−120
3	−11.3	−444
4	−8	−276
5	−129	−960
6	−57	−780
7	−14.7	−528
8	−41.6	−372
9	+2.3	−624
10	+25	−24
11	−50.8	−408

TABLE 2.—*Circulating Platelets after Bleeding of 500 cc. and Replacement with Bank Blood*

Time after Bleeding	Platelets—Per Cent of Normal
2 hours	91
4 hours	96
8 hours	96
1 day	107
4 days	118
8 days	114
11 days	73
14 days	108

operative blood, probably lower even than that of the postoperative blood. This consideration would make the numbers of platelets lost by hemorrhage during the procedure less than recorded and indicates even more strongly that some avenue of platelet losses other than hemorrhage must be sought for.

Table 2 shows the platelet and eosinophil counts of a normal individual bled rapidly of 500 cc. and within one hour transfused with 500 cc. of blood 19 days old, containing 38,000 platelets per cubic millimeter. There is some irregularity of the platelet levels starting four days after bleeding which does not seem to be characteristic of any trend, least of all that of the postoperative state. Since alterations in the platelet count in the direction of a decrease in platelets might conceivably be due to

TABLE 3.—*Alterations in Numbers of Circulating Platelets in Three Patients with Upper Gastrointestinal Hemorrhage*

Days after Onset of Bleeding	Platelet Count in Thousands per cu. mm. Case #			Hematocrit Per Cent Case #		
	1	2	3	1	2	3
1	282			36		42
2	304			30	29	45
3			172	28		45
4			168		23	
5		156		34	24	
6	260		186		29	
7			220			44
8	358	180		34		
9					35	44
10			192			
11						
12		192	278	34	13	
13	292					

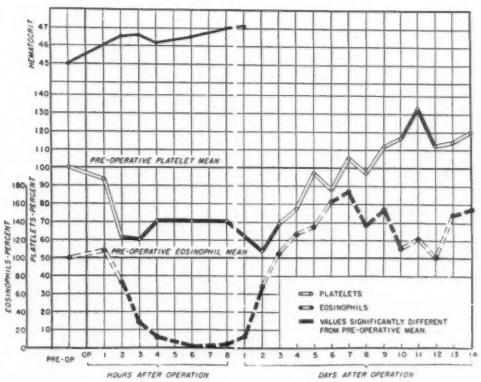

FIG. 2.—Mean platelet and eosinophil counts in nine patients receiving surgical operations.

hemodilution as indicated by the hematocrit, it is of interest to mention that a fall in the hematocrit occurring 50 minutes after bleeding had no effect on the platelet count.

Table 3 shows the changes in the platelet counts of three patients who had varying degrees of gastrointestinal hemorrhage as

indicated and again shows them not to be influenced by hemorrhage of such degree.

Effect of Operative "Stress" on Platelets

Most previous studies of platelets have concerned themselves little with the period during and within the first few hours after operation. Before observing the effect of the stress induced by operation by simulating this effect with corticotropin, it is appropriate to describe better than has heretofore been done the platelet changes, not only from day to day following operation, but from hour to hour following the onset of operation during the operative day. Counts were therefore done pre-

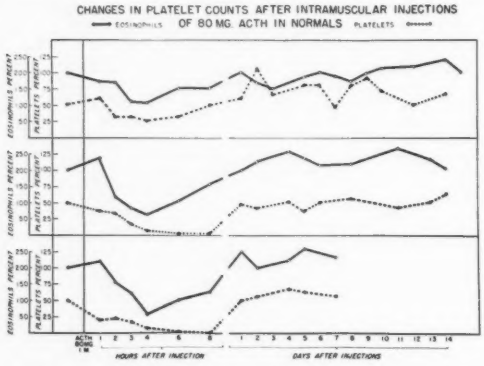

FIG. 3.—Changes in platelet counts after intramuscular injections of 80 mg. cortisone in normals.

operatively, each hour for four hours after the start of operation, every two hours for the next four hours and daily thereafter on nine patients undergoing operations of the standard magnitude described. Figure 2 presents the means of the results. It can be seen that there is a sharp drop of nearly 40 per cent in the platelet count occurring maximally between the second and third hours after onset of operation. The curve then, after a slight rebound, remains low and joins the characteristic previously described curve from the first postoperative day.

It can be seen that hematocrit values alter so little during the period of maximal platelet change that it is doubtful whether any hemodilution can be invoked as the cause of the observed results.

The Effect of Corticotropin on Platelets

The effect on the body of the stress of the operative procedure was then studied by the injection of corticotropin in varying doses by varying routes. Initial studies were performed using corticotropin in 25, 50, 75 and 100 mg. doses by the intramuscular route. In the smaller doses slight decreases of between 5 and 20 per cent were noted in the platelet counts. These decreases became maximal between two and four hours after injection. Larger doses in general showed larger drops of the platelet counts. These observations have already been briefly reported.[9]

For the purposes of further study an intramuscular dose of 80 mg. was then used as one

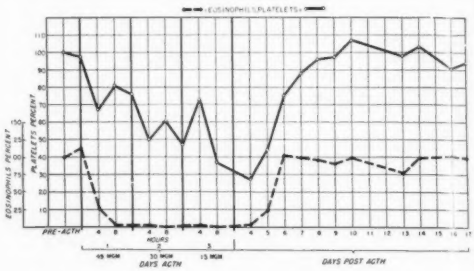

FIG. 4.—Continuous administration of cortisone intravenously for three days. Changes in platelet and eosinophil counts.

which seemed to be the smallest which would give a maximal response. Platelet counts were made in the early hours and for several days after the administration of this dose to normals. Figure 3 shows three characteristic responses. The characteristic fall, up to 43 per cent in these cases, is manifest. There is perhaps a slight tendency towards an immediate rebound but no later prolonged rise as is true after operation.

The consideration of the proper dose of corticotropin to simulate a surgical operation has led us to believe that a single intramuscular dose is but a poor representation of the endogenous hormone elaborated during the procedure. Moore and Hume[11] have suggested that the stress period continues for two or three days after the operation. Accordingly a normal individual was given intravenously and con-

tinuously over a 72 hour period 90 mg. of corticotropin in decreasing concentrations so that he received 45 mg. during the first 24 hours, 30 mg. during the second 24 hours and 15 mg. during the third. Figure 4 demonstrates the platelet and eosinophil responses in this individual. It can be seen that a response is obtained which is nearly similar to that found during the first three days after a surgical operation. There is, however, no thrombocytosis occurring during the second week.

Discussion

The data presented seem to indicate that loss of platelets by the degree of hemorrhage entailed and the types of operations studied is not sufficient to cause the observed changes in the platelet counts. They further show that the platelet falls observed during the first three days after operation can be almost exactly reproduced, even down to their hour by hour changes, by the injection of corticotropin in proper dosages and schedules. Data available so far, however, have not shown a thrombocytosis beginning at the end of the first "postoperative" week after corticotropin, as after operation. Further observations on this score are needed, since if they corroborate these initial ones they will render less tenable the theory that the thrombocytosis of the second week is a compensatory reaction to the early thrombocytopenia. Another cause of the above-mentioned thrombocytosis must then be sought.

It is of course possible that other factors, not so far studied, operate in the early postoperative period to reduce circulating platelets, namely a specific demand on the part of the operative wound for platelets to help with hemostasis in the small vessels of the operative field as described by Zucker[12] and intimated by the work of Lutz and co-workers[13] or possibly a splenic hyperfunction. The use of corticotropin and cortisone to cause thrombocytosis in thrombocytopenic purpura, thought by many to be one form of hypersplenism, would at the present time make the splenic theory an undesirable one.

The mystery surrounding the movements of the formed elements of the blood are nowhere greater than in relation to platelets. We have no better idea of where the platelets go after operation or administration of corticotropin than of where the eosinophils disappear to. In the case of the surgical operation, however, it is our impression, derived from evidence of platelet regeneration in the bone marrow and from increased platelet adhesiveness in the late postoperative period, that platelets have been actually destroyed, not hidden away in some lagoon of the circulation. The same may not be true after corticotropin administration.

Summary

1. Normal individuals losing by hemorrhage 500 cc. of blood were observed to show no change in circulating platelets whether or not the blood shed was replaced with bank blood. No significant alterations in circulating platelets were observed after major gastrointestinal hemorrhage. These results indicate that hemorrhage incurred during operation has little effect on the altered platelet count observed during the postoperative period.

2. The administration of corticotropin exactly mimicked the postoperative thrombocytopenia found during the first three postoperative days. The later thrombocytosis, which may admittedly be the most important element in causing venous thrombosis, could not be so reproduced.

3. Theoretic causes for the thrombocytosis of the second postoperative week are discussed.

Sumario Español

Se analizan los factores que influencian las alteraciones de las plaquetas en la circulación luego de operaciones quirúrgicas. No hay depresión de la médula ósea después de operaciones que pueda explicar la temprana trombopenia ni tampoco la hemorragia operatoria es suficiente para causarla. Evidencia obtenida por medio de la administración de la hormona adrenocorticotrópica sugiere que la hiperactividad adrenal, resultado de esfuerzo de la operación, pueda jugar un papel importante en la temprana trombopenia postoperatoria. La trombocitosis que se observa mas tarde, sinembargo, no fué observada luego de la administración de esta droga.

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Effects of Regitine (C-7337) in Patients, Particularly Those with Peripheral Arterial Vascular Disease

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This is a study of the clinical effects of Regitine, a new antiadrenergic drug, the pharmacologic properties of which are similar to those of Priscoline. Thirty-four patients, whose diagnoses fall into the peripheral vascular disease group and into a miscellaneous group were first given the drug intravenously and the responses were studied with skin temperature recordings in an attempt to predict the response to therapeutic administration of Regitine. The drug was then given orally for varying periods of time, with subjective and objective evidences of response, as well as side effects being noted. The results of these observations are set forth in the paper.

REGITINE, 2-[N-p'-tolyl-N-(m'-hydroxyphenyl) - aminomethyl] - imidazoline HCl, (C-7337), is an antiadrenergic drug first developed by Marxer and Miescher in 1947. Its pharmacologic properties were reported by Meier and Yonkman[1] as being adrenolytic in small doses and sympatholytic in higher concentrations, the latter being reported as greater than that of Priscoline, a progenitor in the imidazoline series. These antiadrenergic properties were tested in man by Hecht, Crandall and Samuels[2] who obtained similar results and added the assumption of local vasodilatation. Studies using direct measurement of blood flow in the femoral artery of the dog demonstrated an increase in blood flow with injections of Regitine, per se, and showed that Regitine is capable of converting the vasoconstricting effect of epinephrine into a vasodilating effect in a dosage of 0.1 to 0.15 mg. per kilogram.[3] Studies on normal students show that Regitine has an efficacy similar to Priscoline in relieving vasospasm induced by cold.[4] It was felt, therefore, that clinical trial of the drug was justified and this report deals with the results of that trial conducted over an 18 months' period. The maximum duration of therapy for any one patient was 14 months, though many are continuing therapy. Most of the patients were given skin temperature studies, testing the drug intravenously, just as were the students.[4] In the clinical evaluation of the drug, it was administered orally and a comparison made between the actual therapeutic response and the initial response to the intravenous injection.

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MATERIAL AND METHODS

Thirty-four patients were studied. They may be divided into four groups, from the point of view of diagnosis, as in table 1, in order to evaluate the results of Regitine therapy in those particular disease states. Group I is comprised of 10 patients with the diagnosis of Raynaud's disease consisting of five females and five males varying in age from 20 to 60 years. Diagnosis of Raynaud's phenomena was considered when several of the following were present: upper or lower extremity involvement, ulceration, when present, limited to tips of digits, secondary sclerodermatous changes, prominent symptoms of coldness, pallor and aching aggravated by cold, changes in nail growth, peripheral pulsations palpable, and on skin temperature study under adequate ganglionic blocking drug shows practically normal maximum temperatures as contrasted to the occlusive diseases.[5] The diagnosis of primary Raynaud's disease was made when the cause was unknown. Two patients were classified as secondary Raynaud's disease in view of possible nerve trunk irritation. In one the symptoms followed myocardial infarction with subsequent shoulder-hand syndrome. In the other the symptoms followed electrical burns to the hands.

Group II is composed of 14 patients with the diagnosis of arteriosclerotic peripheral vascular disease and is made up of 13 males and one female

TABLE 1.

Group I-A—Primary Raynaud's

Case Age Sex	Temperature Studies* Digit	Etamon I.V.	Regitine I.V.	Dosage and Duration	Simultaneous Therapy	Subjective and Objective Response
MMP	*R2F*	*10.0°*	*2.0°*	30–60 mg. t.i.d. for 14 days	Thyroid Ext. 32 mg. Sympathectomy prior to Rx	Left fingers warmed, but still painful with cold weather.
113539	*R3F*	*5.5°*	*3.0°*			
33 yrs.	*R4F*	*7.0°*	*1.5°*			
Female	L3F	17.5°	6.0°			
	L4F	14.0°	9.5°			
RLP	*R2F*		*10.5°*	30–60 mg. t.i.d. for 70 days	Vitamin B_{12} twice weekly	Fingers warmer; cooler when drug withdrawn one week. Small fissure in skin right hand well healed.
117482	*R3F*		*12.0°*			
51 yrs.	L2F		13.0°			
Male	L3F		11.0°	60 mg. q.i.d. for 14 mos.		Fingers warmer and feeling better.
LNJ	*L2F*		*7.5°*	60 mg. t.i.d. for 30 days	None	Fingers staying warm; throbbing and soreness in L2F cleared up. Small abscess L2F healing at last visit.
120757	*L4F*		*10.0°*			
41 yrs.	*L5F*		*8.0°*			
Male	R3F		12.5°			
SRW	R2F	8.5°		30–60 mg. t.i.d. for 25 days	Thyroid Ext. 60 mg. Vitamin B_{12} I.M. 3x/w Thiamine 50 mg. t.i.d.	
124604	R3F	10.5°				
34 yrs.	R4F	11.0°				
Female	L2F	12.5°				
	L3F	11.0°				
	L4F	10.0°				
LBM	*R3F*	*7.5°*	*9.0°*	60–120 mg. 3–4x/d for 2 mos.	Thiamine 50 mg. t.i.d.	Very little pain in R3F or thumb; definitely better. Pricked R3F on thorn, free bleeding for first time in 2 years.
130193	*R5F*	*12.5°*	*12.0°*			
51 yrs.	L3F	11.5°	13.5°			
Female	L5F	13.0°	14.0°			
MPP	R1T	10.5°	1.0°	30 mg. 3-4x/d for 1 mo.	Thiamine 50 mg. t.i.d.	Feet staying warm but legs still ache.
130078	R5T	10.5°	0.5°	90 mg. 3–4x/d for 1 mo.		Feet warmer?
33 yrs.	L1T	9.0°	2.0°			
Female	L5T	11.0°	1.0°			
RSH	L1T	11.5°	0.5°	30–120 mg. t.i.d. for 1 mo.	Thiamine 50 mg t.i.d. Vit. B and C	Better response than to Priscoline. No effect with 30 mg., feet warmer on 60 mg., full relief on 120 mg.
114505	L5T	9.5°	0.5°			
28 yrs.	R1T	9.5°	0 °			
Female	R5T	10.0°	0 °			
ECD	R1T	12.0°	9.5°	30–60 mg. t.i.d. for 9 mos.	Low cholesterol diet, Thiamine 50 mg. b.i.d.	Marked subjective improvement at first, then gradual return of symptoms.
117546	R5T	10.0°	8.0°			
54 yrs.	L1T	12.0°	2.5°			
Male	L5T	10.0°	1.5°			
Group I-B—Secondary Raynaud's Disease						
KWL	*R2F*	*12.5°*	*9.5°*	120 mg. q.i.d. for 2 weeks.	Thiamine 50 mg. b.i.d.	Some warming of hands, but still having pain.
98975	*R4F*	*11.0°*	*10.0°*			
26 yrs.	L2F	11.5°	13.5°	30–120 mg. t.i.d., during very cold weather		Prevented coldness of hands and pain.
Male	L4F	10.5°	12.0°			
FIF	L2F		14.0°	30 mg. t.i.d. for 3 mos.	None	Equivocal. Had bilateral stellate block previously, very little pain on right and less on left.
122219	L4F		13.0°			
60 yrs.	R2F		14.0°			
Male	R4F		14.0°			
Group II—Arteriosclerotic Peripheral Vascular Disease						
PEK	L2F	11.0°	9.0°	60 mg. t.i.d. for 50 days	Vit. B with C, Thyroid Ext. 32 mg./d sympathectomy.	Less coldness and blueness of hands. Prefers Regitine to Priscoline. Evidence of healthier nail growth. Some warming of hands.
114678	L3F	9.0°	10.0°			
46 yrs.	R2F	10.5°	10.0°	Combination of Regitine (60 mg.) and Priscoline (25 mg.) t.i.d., 30 days		
Male	R3F	10.5°	10.0°			
	R1T	1.5°	11.0°			

* Temperature studies in response to either Etamon, 15 mg./Kg. or to Regitine, 0.5 mg./Kg., intravenously, prior to starting oral therapy. The italicized figures are the responses of the affected extremities; the nonitalicized figures are the responses of the unaffected opposite normal extremity. The responses are expressed as the maximum temperature reached in the extremity in response to the drug administration, expressed in degrees centigrade above the room temperature of 20°C.

Digit abbreviations: R—right; L—left; F—finger; T—toe; numeral indicates digit position.

The following patients had blood cholesterol values greater than 200 mg. per 100 ml.: group IB, FIF; group IIA, PEK, JPT, RVA, HM, HGP, CDF, TLP, JGN, EAH; group II, WDM, HJW; group III, ANT; group IV, CHM.

TABLE 1.—*Continued*

Group II—Arteriosclerotic Peripheral Vascular Disease—Continued

Case Age Sex	Temperature Studies*			Dosage and Duration	Simultaneous Therapy	Subjective and Objective Response
	Digit	Etamon I. V.	Regitine I.V.			
)HO (820 (1 yrs. Male	L1T L5T R1T R5T	1.5° 1.0° 0.5° 0.5°	7.0° 7.0° 2.5° 4.0°	30 mg. t.i.d., 5 days 60 mg. t.i.d., 2 weeks 30 mg. t.i.d., 9 mos.	Phlebotomy for polycythemia	"Feet and legs haven't hurt for 3 months." No recurrent leg pain.
JPT 103336 52 yrs. Male	L1T L5T R1T R5T	0.5° 0 ° 0.5° 0 °	3.0° 2.5° 0.5° 1.0°	60 mg. t.i.d., for 3 mos.	Right and left lumbar sympathectomy, low cholesterol diet, vit. B with C, Lipocaps, 3, q.i.d., Thiamine, 50 mg. b.i.d.	No relief of leg pain. Subsequent amputation of left lower extremity. Ulcer on right foot disappeared, extremity no longer painful.
RVA 114051 58 yrs. Male	L1T L5T R1T		9.5° 8.5° 8.5° 7.5°	60 mg. t.i.d.	Low cholesterol diet, Lipocaps, 3, t.i.d., Thyroid 32 mg./d.	
HMc 103162 51 yrs. Male	L1T L5T R1T R5T		8.0° 10.0° 10.0° 11.0°	30–60 mg. h. s.	Thyroid Ext. 16 mg. Low cholesterol diet, Lipocaps 3, t.i.d.	Stops aching in legs that formerly kept him awake.
HGP 103162 51 yrs. Male	L1T L5T R1T R5T	6.0° 7.5° 7.5° 9.5°	9.0° 3.0° 1.5° 0 °	60 mg. t.i.d. for 10 mos.	Low cholesterol diet, Lipocaps, 3, t.i.d.	Feet still cool at night but less than formerly.
CDF 125344 64 yrs. Male	R1T R5T L1T L5T	1.0° 1.0° 1.0° 3.0°		60 mg. t.i.d	Lipocaps, 2, t.i.d.	
TLP 48253 36 yrs. Male	R1T R5T L1T L5T	7.0° 8.5° 8.5° 9.0°	6.5° 9.0° 9.0° 8.0°	60 mg. t.i.d for 3 mos.	Diabetic regime	Pain in legs relieved except when out of drug for short time. Feet warmer to touch.
JGN 128494 70 yrs. Male	R1T R5T L1T L5T		3.0 4.5 5.0 8.0	30 mg. 3–4 times/day	Lipocaps, 3, t.i.d.	No help for calf pain or sores, right leg. Subsequent amputation right leg.
GFS 121493 57 Male	R1T R5T L1T L5T	5.5 7.0 3.0 9.0	0 1.0 0 0.5	30–60 mg. 3–4x/d for 3 mos.		Gives warmth in feet. When not taking drug, legs not good and sleeps poorly.
RWS 121493 83 yrs. Male	R1T R5T L1T L5T	1.0° 2.0° 1.5° 2.5°	2.0° 4.5° 2.0° 3.5°	60 mg. q.i.d for 3 mos.	Low cholesterol diet, Lipocaps, 2, t.i.d., left lumbar sympathectomy	No further pain; leg and foot improved.
E H 104760 60 yrs. Female	R1T R5T L1T L5T	12.5 10.5 13.0 8.5	9.0 8.0 10.5 7.5	30 mg. t.i.d. for 14 mos.	Lipocaps, 2, b.i.d. Vit. B with C, Thiamine 50 mg. b.i.d.	Feet better; no longer cold after 8 months. Leg pain when out of drug temporarily, improving with reinstitution.
Arteriosclerotic Peripheral Vascular Disease with Sudden Thrombus Formation						
W M 10 50 59 rs. M e	R1T R5T L1T L5T	0.5 0.5 5.0 2.5		60 mg. q.i.d. for 4 mos.	Low cholesterol diet, Lipocaps, 3, t.i.d , B complex with C, Thyroid 32 mg./d. Left lumbar sympathectomy	Relieved for several months. Subsequent acute occlusion involving left foot with eventual amputation of both legs.
H W 68 57 80 rs. M e	R1T R5T L1T L5T		7.0 7.0 2.5 7.0	60 mg. q.i.d. for 2 mos. 60 mg./day for 4 mos.	Low cholesterol diet, Vit. B with C, Lipocaps, 2, t.i.d.	Feet staying comfortable. Feet staying warm.

TABLE 1.—*Continued*

Group III—Thromboangiitis obliterans

Case Age Sex	Temperature Studies* Digit	Etamon I. V.	Regitine I.V.	Dosage and Duration	Simultaneous Therapy	Subjective and Objective Response
ANT 20211 63 yrs. Male	R1T R5T L1T L5T	8.5 6.0 5.5 6.5	7.0 6.5 6.0 8.0	120 mg. q.i.d. for 4 wks.	Low salt diet, Vit. B with C	Fingers and toes remaining warm while on drug. Draining ulcer under L3T granulating while on drug; enlarged when discontinued therapy due to nausea.
IAH 126475 40 yrs. Male	R1T R5T L1T L5T	3.5 5.5 9.5 11.5	1.5 5.0 10.0 9.0	120 mg. q.i.d. for 10 mos.	Thiamine 50 mg. t.i.d. Vit. B with C	Relief of pain in right foot, but no subjective warming of that foot. Ulcer tip of R1T healed approximately 30 days. Evidence, also, of new nail growth.
JMc 113282 41 yrs. Male	L1T L5T R1T R5T	1.0 0 2.0 1.0		30-60 mg. t.i.d., p.r.n., for pain in foot—2 mos.		No benefit. Went on to gangrene right leg.

Group IV—Miscellaneous

Anxiety reaction with vague aches and pains SAG 58028 56 yrs. Female	No temperature studies			60 mg. t.i.d., for 1 mo.	None	Helping aches in arm and coccyx.
Acute edematous pancreatitis MLG 86602 21 yrs. Female	No temperature studies			30 mg. t.i.d., for 2 mos.	Fat free diet, Splanchnicectomy prior to therapy	
Trauma to ankle with prolonged pain and swelling CHM 72256 52 yrs. Female	No temperature studies			30 mg. t.i.d. for 2 wks.	Low cholesterol diet. Heat and elevation	"Improved."
Bilateral thrombophlebitis, superficial calf veins GBF 3812 36 yrs. Female	L1T L5T R1T	5.5 5.0 5.0	3.0 1.0 7.0	30 mg. t.i.d. for 6 ds. plus	Alpha tocopherol 100 mg./d, elastic bandages	No benefit.
Low back pain AHW 55473 58 yrs. Female	No temperature studies			30–120 mg. t.i.d. for 2 mos.	Reduction diet, Vit. B with C, Thiamine 50 mg. b.i.d., local heat	Back pain relieved.
Causalgia MJMc 126463 31 yrs. Female	R2F R5F L2F R1T R5T L1T		9.0 10.0 12.0 1.0 0.5 1.0		Thiamine 50 mg. t.i.d.	No benefit, symptoms as before.
Chronic thrombophlebitis NM 5869 51 yrs. Female	R1T R4T L1T L4T	11.0 6.5 8.5 12.0	5.0 1.0 6.0 2.0	60 mg. q.i.d. for 12 days 90 mg. t.i.d. for 1 mo. 60–120 mg. HS	Sympathectomy prior to therapy	Relief of aching and redness. "Doing well"

* See footnote on page 488.

varying in age from 46 to 83 years. Diagnosis was made on the following criteria: usually 40 years of age or older, limited to lower extremities, absent peripheral pulsations, duration two to three years or less, blood cholesterol 220 mg. per 100 ml. or higher, Gofman Sf 10–20 molecules 35 mg. per 100 ml. or above and Sf 20–100 molecules 55 mg. per 00 ml. or more, calcification of the blood vessels of the leg when present (absence not excluding), evidence of atherosclerotic changes elsewhere (coronaries, brain, xanthoma palpebrarum), usually, but not always, pain, blanching, intermittent claudication, dependent rubor and prolongation of return of color on return of foot to heart level after elevation of the foot for 30 seconds. Two patients of this group suffered sudden arterial occlusion by thrombosis secondary to arteriosclerosis. PEK, 114578, was included in this group because of the x-ray evidence of calcification and elevated blood concentration of cholesterol and Gofman molecules,* but one is forced to make a diagnosis of Raynaud's disease of unknown cause to explain changes in upper extremities.

Group III is composed of three patients with the diagnosis of thromboangiitis obliterans, all being males, aged 40, 41 and 63 years. Criteria for diagnosis in this group were: age, combined involvement of hands and feet and obliteration of peripheral pulsations. Symptoms and physical examination were otherwise essentially the same as those of arteriosclerosis; there was an absence of elevated blood cholesterol and of calcification of the blood vessels of the legs.

Group IV is composed of seven females ranging in age from 21 to 50 years with miscellaneous disorders varying from anxiety to acute pancreatitis.

Prior to administration of Regitine† orally on a therapeutic basis, an attempt was made to ascertain first the effect of the drug on the peripheral circulation of the patient by skin temperature studies. Since both vasospasm and organic occlusion are usually present in peripheral vascular disease, both the degree of occlusion and the probable degree of effectiveness of a vasodilator drug in overcoming the vasospasm can be determined by measurement of the increased skin temperature consequent to an augmented rate of delivery of heat to the skin resulting from the increase in cutaneous blood flow produced by the vasodilator drug. Records of the cutaneous temperature were made with an 8-point Leeds and Northrup micromax using iron constantin thermocouples attached to the skin with a drop of collodion. During the study, the patients were placed in a room, the temperature of which was maintained at 19 to 20 C. The cutaneous areas to be measured were exposed to the room air and care was taken to avoid contact or close approximation of any objects which might prevent rapid circulation of air past the exposed parts. Temperatures were recorded usually over the forehead, index and fourth fingers, great and little toes, together with the room temperature. Blood flow and vasoconstriction were estimated from the relationship of the temperature of the skin to that of the room and forehead temperatures. Minimal blood flow due to maximal vasoconstriction was considered to be present when the skin temperature approximated room temperature and maximal blood flow due to maximal vasodilation when the skin temperature approximated or exceeded the forehead temperature. Regitine was injected intravenously over a 30 minute period in amounts up to 0.5 mg. per kilogram, dissolved in 250 ml. of normal saline; the total amounts given varied from 20 to 50 mg.

In a further attempt to correlate the predicted response to Regitine with the actual therapeutic response, additional temperature studies were done using Etamon (TEA),‡ as it was felt that the fraction of effectiveness of Regitine to Etamon may represent the expected response as compared with full release of vasospasm by Etamon. These studies were carried out on 18 of the patients, the records of which are included in table 1. Etamon was injected under the same conditions as was Regitine, in the amount of 15 to 20 mg. per kilogram dissolved in 250 ml. of normal saline. The maximum dosage used was 1,732 mg. and the minimum was 645 mg.

For administration to the patients for evaluation of therapeutic response, Regitine was given orally and on an individual basis for each patient. Dosage and duration of trial are recorded in table 1, the dosage varying from as little as 30 mg. once a day to a maximum of 120 mg. four times a day, before or after meals, depending upon side effects. The maximum duration of trial was 14 months and the minimum was two weeks.

Simultaneous therapy is recorded for each patient in table 1 in order that no factors be overlooked which might affect the clinical response to Regitine. Evaluation of response to the drug was, of necessity, purely subjective in the majority of patients, though in some, subsequent healing of previously chronic lesions, healthier nail growth and increased walking distance afforded objective evidence of benefit. Both subjective and objective responses to the drug are recorded in table 1.

Pertinent accessory clinical findings were recorded,

* Gofman molecule (lipoprotein) determinations were done by Belmont Medical Laboratories, Inc., Belmont, Calif.

† The oral and intravenous preparations were kindly supplied by Dr. F. L. Mohr of Ciba Pharmaceutical Products, Inc., Summit, N. J.

‡ Kindly supplied by Dr. E. C. Vonder Heide of Parke, Davis and Company, Detroit 32, Mich.

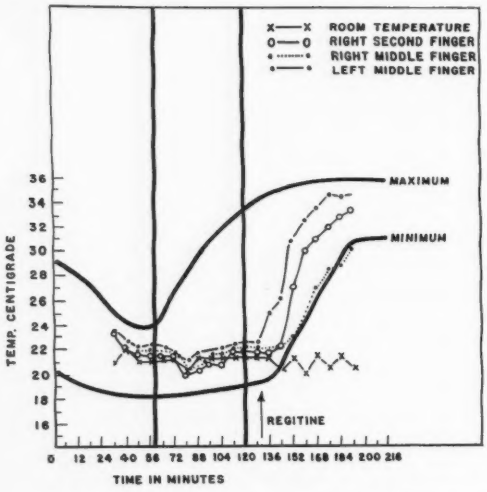

FIG. 1. Temperature changes in the fingers of LBM, 130193, in response to 29.7 mg. (0.5 mg. per kilogram) of Regitine. Her complaint was recurring pain in the fingers of the right hand upon exposure to cold. Her diagnosis was primary Raynaud's phenomena. This response was considered a good one and the patient obtained a good response to oral administration. (See also table 1.)

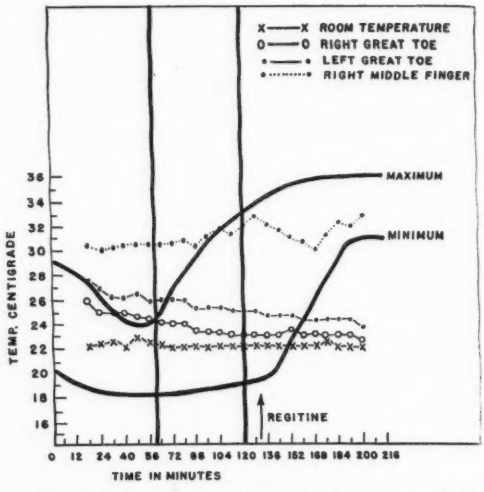

Fig. 2. Temperature changes in the right and left great toes and right middle finger of JPT, 113336, in response to 30.6 mg. (0.5 mg. per kilogram) of Regitine. His complaints were those of intermittent claudication and swelling of the lower extremities. His diagnosis was arteriosclerotic peripheral vascular disease. This response was considered a poor one and the patient experienced neither subjective nor objective improvement with oral administration of the drug. (See also table 1.)

TABLE 2.—*Predicted Response on Basis of Comparison with TEA or of Unaffected Part*

Group	Good Response	Fair Response	Equivocal	No Temperature Study	Poor Response
I	RLP-LBM-FIF	LNJ-KWL-SRW	MMP-ECD		MPP-RSH
II	PEK-DHO-TLP-RWS	RVA-HMc-HJW-EAH	JGN		JPT-HGP-CDF-GFS-WDM
III	ANT-IAH				JMc
IV		GBF-NM		SAG-MLG-CHM-AHW	MJMc

TABLE 3.—*Results of Regitine Therapy*

Group	Objective Evidence of Improvement	Subjective Improvement	Equivocal	No Follow Up	No Benefit
I	LNJ-RLP-LBM	RLP-LNJ-LBM-RSH-KWL	MMP-MPP-FIF	SRW	ECD
II	PEK	HGP-PEK-DHO-HMc TLP-GFS-RWS-HJW EAH		RVA-CDF	JPT-WMD-JGN
III	ANT-IAH	ANT-IAH			JMc
IV		SAG-CHM-NM	AHW	MLG	GBF-MJMc

both for substantiation of the diagnosis and for determination of the effect upon any blood elements as previously reported by Hecht and Grandall.[2] An attempt was made to obtain hemoglobin, white blood cell count and differential white blood cell determinations before and after beginning therapy with Regitine on as many patients as possible.

In order to predict the response of a given patient to the therapeutic trial with Regitine, the degrees rise in skin temperature of the part above room temperature was used as an index to the extent to which intravenous Regitine overcame the maximal vasoconstriction of the part obtained as described above. This was also a measure of the amount of vasospasm present in the particular disease process, and in those in whom little or no increase in skin temperature of the affected part occurred, a similar poor response was predicted in the therapeutic trial. Figure 1 illustrates a good response in skin temperature study, and figure 2 illustrates a poor response. Table 2 summarized the predicted responses for the individual patients and by groups, based on the abstracted skin temperature studies recorded in table 1.

Results

The responses actually obtained by the individual patients are recorded in table 1 and summarized in table 3, again on an individual and group basis. Simultaneous therapy, particularly sympthectomy, must be considered in an evaluation of results. There were five patients who underwent sympathectomy prior to use of Regitine, two during the course of treatment with Regitine, and one was done after Regitine was discontinued. It was necessary to stop Regitine on the latter patient, ANT 20211, because of an episode of acute vasomotor collapse. It is to be noted that in only one patient, MMP, 113539, of the Raynaud's disease group, was sympathectomy done and this was prior to Regitine trial. The two patients undergoing sympathectomy during their trial on Regitine were both in the arteriosclerotic group: WMD, 100950, had suffered sudden thrombus formation; poor response was predicted, of course, and subsequent amputation was necessary. The other, PEK, 114678, underwent sympathectomy because it was necessary to discontinue the drug therapy since he developed a rash while taking the drug. A good response to Regitine had been predicted from the temperature studies and had been obtained with the drug; the response to sympathectomy was satisfactory.

Correlation between the predicted and actual responses obtained was fairly good, but in several cases it was not possible to obtain a follow-up and these cannot be considered in the evaluation of the drug.

When studied by disease groups, approximately 58 per cent of the arteriosclerotic group was predicted to get fair to good response and obtained objective and/or subjective response in approximately 64 per cent. This represents a much higher percentage than would be anticipated from the nature of the disease. The Raynaud group, in whom good results might be anticipated, showed 63 per cent good or fair predicted responses, and 50 per cent showed comparable actual response. The results in the thromboangiitis group were encouraging, though the size of the group was too small to be of any value in the evaluation of the drug in this disease. The results obtained in group IV were variable as might be anticipated from the assortment of diagnoses, and temperature studies were not obtained on four of the seven. However, a fair response was predicted for two patients of this group, GBF 3812 and NM 5869, both of whom had chronic thrombophlebitis, but only one showed subjective improvement on Regitine therapy.

In a comparison of the vasodilating effect of Regitine and Etamon, it was found that 10 patients responded with higher average skin temperatures, in parts tested, to Etamon than to Regitine. Of this group, four were in the Raynaud group, three were in the arteriosclerotic group, two had chronic thrombophlebitis and one was in the thromboangiitis group. The response to Regitine was greater in five, and the two drugs produced essentially the same amount of skin temperature rise in three. Four of the five who showed a better response to Regitine were in the arteriosclerotic group, and of the two who obtained essentially equal responses, one was in the arteriosclerotic group, the other was in the thromboangiitis group.

Side effects noted during the therapeutic trial with Regitine are listed below in order of frequency of occurrence. The frequency was

calculated as the percentage of patients experiencing a particular side effect, with many experiencing several of the reactions. It was necessary for seven of the patients to discontinue the drug entirely due to side effects. The total number of patients was 34.

Diarrhea	26%	
Nasal stuffiness	24%	
Dizziness	24%	
Nausea	18%	
Weakness	9%	
Vomiting	9%	
Palpitation	9%	
Chilliness	6%	
Nervousness	6%	
Dyspnea	6%	
Vasomotor collapse	6%	
Drowsiness	3%	(1 patient)
Itching sensation deep in volar surface of forearm	3%	(1 patient)
Petechial rash	3%	
Total incidence of side effects	62%	

Vasomotor collapse, the only side effect of any magnitude, occurred in two patients, ANT, 20211 and WDM, 100950. It occurred within a few minutes in one and approximately two hours in the other after administration of 60 mg. of the drug orally (the former was about three hours, the latter, approximately 30 minutes postprandial). The reaction was preceded by nausea and vomiting, and was then manifested by apprehensiveness, a sudden temperature elevation to 100^4 to 100^8 F. with a shaking chill, pallor, cold and clammy skin, blood pressure drop (from 140 mm. Hg systolic over 84 mm. Hg diastolic to 80 systolic over 70 diastolic in one, and from 180 systolic over 90 diastolic to 110 systolic over 80 diastolic in the other), and was followed by weakness and diarrhea. Both of the patients were in the hospital at the time of occurrence, and the reactions were successfully managed by Trendelenberg position and intravenous glucose, with full recovery and return of blood pressures to former levels in three to four hours. A blood sugar determination done on ANT, 20211 prior to administration of intravenous glucose was reported as 99 mg. per 100 cc. There was no change in any aspect of the hemogram.

Discussion

The ability of Regitine to produce cutaneous vasodilation in animals and in normal students has been confirmed in this study on patients. This effect is probably produced by blocking the sympathetic constrictor impulses and in this respect is somewhat less effective than Etamon. However, correlation between the response predicted by study of the intravenous administration of Regitine and that obtained on oral administration appears to be good in the individual patient, but contradictory for the disease groups. It would be anticipated from the nature of the disease and pharmacologic properties of Regitine, that patients with Raynaud's disease would get better response than those with occlusive disease. However, percentage-wise the actual response of the Raynaud group was much poorer than either the arteriosclerotic or thromboangiitic groups. It is interesting to note also that all but one of the patients who got a better or equal response to Regitine in comparison with Etamon, were in the arteriosclerotic group. An explanation of these somewhat paradoxical results would be difficult, but would seem to justify further study.

In a comparison of the subjective and objective effects of Regitine and those reported for Priscoline by Grimson and colleagues in 1948,[6] it appears that Regitine is somewhat inferior to Priscoline in its effects upon patients with Raynaud's disease. On the other hand the results with Regitine were more encouraging than those with Priscoline in patients with arteriosclerotic peripheral vascular disease and those with thromboangiitis obliterans. Responses in the miscellaneous group of patients were equivocal in both studies. Though no frequency of side effects was reported for Priscoline, our own experience with this drug indicates that many patients complain severely of chilliness, pruritis of the scalp, pilomotor reactions, conjunctival injection and gastrointestinal reactions. Those experienced with Regitine are apparently significantly less than those of Priscoline with the exception of the vasomotor collapse occurring in two patients receiving Regitine, and a mild petechial rash seen in one patient. No significant changes in white blood counts have been noted by us during prolonged therapy with either Regitine or Priscoline.

In analyzing the two cases of vasomotor

collapse, it is difficult to explain the occurrence in these two patients and yet in none of the others. Less marked symptoms of hypotension were reported in a fairly large percentage of patients. Trapold and Warren[7] have attributed reactions to Regitine to a lowering of the blood sugar level. However, the blood sugar determination done on one of the patients experiencing the vasomotor collapse was within normal limits for what was essentially a three hour postprandial level, and though there is no record of a previous determination there was no evidence of preceding hyperglycemia. The blood pressures in the two showed the typical wide pulse pressures of arteriosclerosis; the drop was predominantly systolic, suggesting a sudden reduction in stroke volume output by the heart. It is of significance that each subject had previously been taking the drug for several days before the reactions were first noted; in other words, a sensitivity seemed to have developed after prolonged use of the drug. It seems that there is no way of predicting such a reaction, or preventing it by regulating administration by meals or otherwise. However, it is easily managed by Trendelenberg position, intravenous glucose, the glucose being recommended on the basis of the earlier study referred to above, and, of course, discontinuance of the drug.

It is concluded that a trial on Regitine therapy is indicated before resorting to sympathectomy in any peripheral vascular disease as only three patients in this study underwent sympathectomy during or after Regitine therapy, and treatment has been maintained as long as fourteen months. It is a valuable adjunct after sympathectomy, and in the dose range of 30 to 60 mg. two to four times a day is tolerated with relatively few serious side effects in the majority of patients.

Summary

1. Regitine, a new antiadrenergic drug, has been shown to have both adrenolytic and sympatholytic properties; its ability to relieve vasospasm induced by cold being approximately equal to that of Priscoline. This paper deals with the clinical trial of Regitine, felt to be justified by previous studies.

2. Thirty-four patients were studied: 10 with Raynaud's disease, 14 with arteriosclerotic peripheral vascular disease, three with thromboangiitis obliterans and seven with miscellaneous diagnoses.

3. The patients were first tested with Regitine intravenously while skin temperatures were recorded, in order to ascertain the effect of the drug on the peripheral circulation of the patient. The response shown, and, in many cases, compared with a skin temperature study with Etamon, was used to predict the therapeutic response to Regitine.

4. Regitine was administered orally in doses ranging from 30 mg. once a day to 120 mg. four times a day. The maximum duration of trial was 14 months and the minimum was two weeks. Evaluation of the response was largely subjective, but in many, objective evidence was present.

5. Correlation between the predicted and the actual response obtained was good in the individual patient, but contradictory for the disease groups. Thus, the patients in the arteriosclerotic group appeared to obtain more benefit from the oral administration of the drug than did the Raynaud group. Results in the thromboangiitis group and in one patient with chronic thrombophlebitis were encouraging.

6. Serious side effects were few, the only reaction of any magnitude being vasomotor collapse which occurred in 2 of the 34 patients receiving the drug; however, minor side effects were noted by 62 per cent of the patients.

7. Regitine appears to be a useful adjunct to treatment of peripheral vascular diseases and is felt to be indicated prior to consideration of sympathectomy. Furthermore it is useful in subsequent treatment of cases which have undergone sympathectomy.

Sumario Español

Este es un estudio de los efectos clínicos de Regitine, una nueva droga anti-adrenérgica, las propiedades farmacológicas de la cual son similares a las de Priscoline. Treinta y cuatro pacientes, cuyos diagnósticos entran en el grupo de enfermedades perifero vasculares, y en un grupo misceláneo se les administró la droga intravenosamente y los resultados fueron estudiados mediante determinaciones de temperatura

cutánea en un atentado a predecir el resultado terapéutico al administrar Regitine. La droga fue luego administrada oralmente por intervalos variables de tiempo con evidentes resultados subjetivos y objetivos al igual que efectos secundarios no deseables que también fueron observados. Los resultados de estas observaciones se presentan en este trabajo.

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Recurrent Parietal Thromboendocarditis

By Campbell McNicol, Capt., M.C., H. Edward MacMahon, M.D., A. S. Benenson, Lt. Col., M.C., and Theodore Winship, M.D.

A rare condition, which generally occurs in young adults and may simulate coronary disease, is discussed. The patients are afebrile, with low blood pressures, fast weak pulses and marked irregularities in cardiac rhythm. They are unresponsive to therapy and may survive initial attacks only to succumb to a recurrence. In the portions of the endocardium uninvolved by mural thrombi, there is marked collagenized subendocardial thickening devoid of elastic tissue. The etiology is unknown.

THE PURPOSE of this report is to describe two cases of a relatively rare and obscure endomyocardial affection, occurring in young adults, which appears to stem from varying degrees of endocardial thickening. This type of pathologic lesion gives rise to a fairly definite clinical picture, which, while nonspecific, is nevertheless to be considered in cases of atypical subacute to chronic myocardial failure in the absence of demonstrable coronary or valvular disease, either clinically or at autopsy. The lesion consists of collagenous thickening of the subendocardial connective tissue with superimposed ulceration of the overlying endocardium. This is followed by a florid proliferation of the subendocardial connective tissue into the trabeculae carneae and along the vascular septa of the myocardium, with eventual mural thrombus formation and its sequelae of peripheral embolization.

Case Reports

Case 1.

A 34 year old white man was admitted to Murphy General Hospital on July 28, 1948, with shortness of breath on exertion, weakness, nocturnal dyspnea, weight loss, and pain in the paraumbilical region of the abdomen occurring two to three hours after meals.

At the age of 12, cervical lymph nodes on the left side had been removed for "swelling." The diagnosis on the removed nodes is not known. No further lymphadenopathy was noted. In 1946 he first complained of recurrent abdominal pain following meals and the diagnosis of duodenal ulcer was made. He received treatment for this condition and was again admitted to the hospital in 1947. Electrocardiograms taken at that time were abnormal, but no definitive diagnosis of heart disease was made. On further questioning, the patient stated that he had been told in 1942 that he had "heart disease" but did not know what diagnosis had been made. There was no past history of rheumatic fever or syphilis.

From 1946, the symptoms of chronic cardiac failure became progressively worse.

Physical examination, on admission, revealed a pulse rate of 132, blood pressure 90/70, and no dyspnea at rest. The heart was enlarged to the left, and to a lesser extent to the right. The pulse was weak, threadlike, and gallop rhythm was heard at the apex. No murmurs or friction rubs were observed. The lungs were clear, and there was no fluid in the abdomen. The liver edge was palpable below the right costal margin. The remainder of the physical examination was noncontributory. Fluoroscopy of the heart on July 29, 1948, was considered fairly characteristic of pericardial effusion. His admission electrocardiogram showed marked left axis deviation and inversion of all T waves. This was almost identical to the electrocardiographic findings six months earlier. The initial impression was pericardial effusion, probably of a tuberculous nature. Later electrocardiograms taken Sept. 20, 1948 disclosed findings consistent with pericarditis (fig. 1).

The laboratory findings on admission showed a hemoglobin of 80 per cent, a white blood cell count of 10,700 with a normal differential, hematocrit of 43, and a sedimentation rate of 24 mm. in one hour. Urinalysis showed a specific gravity of 1.028 and a trace of albumin. It was otherwise normal. Serology was negative. Repeated sputum examinations for tubercle bacilli were negative. The total protein was 5.3 mg. per cent. Chest roentgenologic examination in August 1948, revealed an enlarged heart with evidence of right lower lobe pneumonia. On Feb. 4, 1949, there were scattered areas of pneumonic infiltration in both lower lobes with the possibility of superimposed pulmonary infarction.

The clinical findings, together with a history of cervical adenopathy in childhood, a positive tuberculin test, and slight apical infiltrations by x-ray examination, led to the institution of streptomycin therapy on the basis of a probable tuberculous pericarditis. This therapy, however, did not alter the course of the disease, and despite digitalis and supportive measures, the patient failed to improve. There were recurrent acute attacks of dyspnea and

tachycardia. His pulse rate varied from 80 to 160 during the hospital course, with average rates of 100 to 120. On Jan. 25, 1949, clinical thrombophlebitis involving the right leg was discovered. The prothrombin time was markedly prolonged, being only 16.4 per cent of normal, and anticoagulant therapy was begun cautiously and then stopped because of apparent liver damage. Repeated prothrombin times were essentially the same, and the patient evidenced clinical jaundice for the first time on Jan. 30, 1949. The liver was tender and extended four finger breadths below the right costal

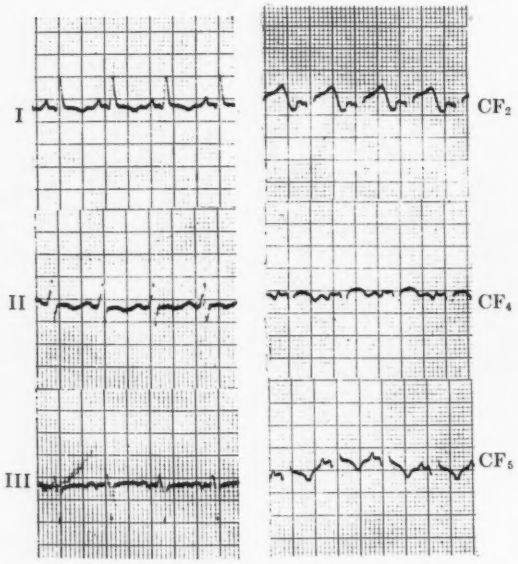

FIG. 1. There is left axis deviation with sinus tachycardia. T waves are inverted in leads I, II, and CF_5; diphasic in CF_2 and CF_4.

margin. On Feb. 8, 1949, he developed severe dyspnea, stupor, and finally expired.

Gross Necropsy Findings. The heart weighed 330 Gm. A gray, fibrous membrane covered the epicardial surfaces of both ventricles, and the pericardial cavity contained about 80 cc. of clear, bile-stained fluid. The chambers were dilated. The myocardium was flabby and pale tan-yellow in color. The parietal endocardium of the left ventricle was covered with a layer of adherent, gray, opaque fibrous tissue with massive mural thrombus formation at the apex. The coronary arteries were normal in origin and distribution, and were widely patent throughout. *The valves were normal.* There were no verrucae or vegetations. The left ventricular wall measured between 12 and 16 mm. in thickness, and the right 2 to 4 mm. The right lung weighed 900 Gm. A large, firm, reddish brown, wedge-shaped area was noted in the right upper lobe. Two similar but smaller areas were present in the right lower lobe. Adherent thrombi, occluding the lumina, were found in branches of the pulmonary artery leading to these areas. The left lung weighed 550 Gm. and, on section, large quantities of edema fluid oozed from the cut surfaces. The liver weighed 1270 Gm. and on section had a "nutmeg" appearance. The spleen weighed 150 Gm. and was moderately congested. The right kidney weighed 160 Gm., the left 145 Gm. Neither kidney was grossly remarkable. The gastrointestinal tract was normal, with the exception of an old healed duodenal ulcer. The remaining organs, with the exception of the brain, which was not examined, were normal.

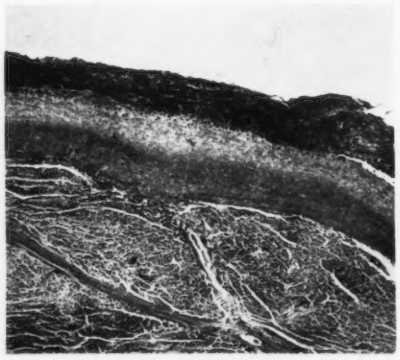

FIG. 2. Case 1. There is a superficial layer of fibrin. Beneath it the subendocardial collagen is thickened. (Mallory aniline blue stain, ×35.)

Microscopic Findings. The lining serosal cells of the epicardium showed considerable hypertrophy, assuming a somewhat polygonal to cuboidal form with fairly large, vesicular, round to spherical nuclei. Sparse lymphocytic infiltrations were noted. One section, through all coats of the right ventricle, disclosed a rich hyperplasia of collagenous connective tissue involving the epicardial fat in one area, and strongly resembling that seen in the endocardium. There was slight myocardial edema, and focal zones of sclerosis were evident in the subendocardial areas. Little or no sclerosis was seen in the deeper myocardium. The subendocardial collagenous connective tissue was markedly thickened. (See fig. 2.) In some areas it was fairly cellular; in others, it assumed the appearance of a somewhat amorphous ground substance. Special stains revealed that this increased thickness was due to the deposition of large quantities of collagen in the subendocardial region. There was practically no elastic tissue at this site. The collagen in this location was similar to that composing the underlying bands which extended into the myocardium along the perivascular connective tissue septa. There was a large organizing

thrombus composed of large masses of red cells, fibrin, proliferating small blood vessels, and numerous lymphocytes overlying the thickened endocardium (fig. 3). Islands of persisting viable myocardium were pinched off and surrounded by collagenous connective tissue. Similar thrombi filled the bays and extended into the thebesian veins.

Chronic passive congestion, atelectasis, and hemorrhagic infarction were demonstrable in the lungs. The liver showed severe chronic passive congestion with hemorrhagic central necrosis. There was moderate chronic passive congestion of the pancreas, spleen, and kidneys. The adrenals showed slight lipid depletion and congestion. Chronic inflammation of the stomach and duodenum was

FIG. 3. Case 1. Discloses mural thrombus with underlying thickened endocardium. (Hematoxylin and eosin stain, ×35.)

present. A section of omental fat revealed a sclerotic thickening of the serosa.

Case 2.

A 27 year old white man was admitted May 2, 1950 to the hospital at Fort George G. Meade, Md., with abdominal pain of approximately one month's duration, followed by ankle swelling and dyspnea of 10 days' duration. There was no past history of rheumatic or venereal disease. He was well until approximately one month prior to admission at which time there was an abrupt onset of persistent postprandial nausea and vomiting of undigested food, followed later by generalized aching abdominal pains. Ten days prior to admission he noted mild dyspnea without orthopnea, followed by swelling of the lower legs and ankles. Physical examination on admission disclosed a temperature of 97 F., an imperceptible pulse with an apical rate of 136, respirations of 20, and an unobtainable blood pressure. He was acutely ill, with slight cyanosis of the lips, reddish-purple blotches on the skin, a generalized, excoriated, maculopapular rash, and a few small ecchymoses. Chest examination revealed a few moist rales at the bases, and the heart was slightly enlarged to the left. The sounds were fairly sharp with a gallop rhythm heard best at the apex. No murmurs were noted. There was generalized abdominal tenderness and slight distention. The liver was palpable two finger breadths below the right costal margin. The penis was edematous, and there was 4 plus pitting edema as high as the knees and to a lesser extent over the thighs and abdomen.

He was placed on oxygen, digitoxin, and Mercuhydrin therapy, but failed to respond. The tachycardia, gallop rhythm, edema, and rales persisted. Blood pressures varied between 75/60 and 90/80. On May 9, 1950, he first showed persistent clinical jaundice. On May 20, 1950, he vomited 500 cc. of fresh and clotted blood, and died shortly thereafter.

Gross Necropsy Findings. On external examination, the body was that of a well developed, rather obese, 27 year old white male, weighing approximately 225 pounds and measuring 68 inches in length. There were 250 cc. of clear amber fluid in the peritoneal cavity. The stomach was markedly distended and the appendix absent.

The heart weighed 430 Gm. and the pericardial cavity contained 90 cc. of clear amber fluid. The myocardium proper presented no gross lesions. In the apical area of the left ventricle, a friable, pinkish-white opaque mass, measuring 1.5 cm. in diameter, was attached to the endocardium. A similar mass of friable tissue presented on the right auricular endocardium, and measured 1.0 by 1.0 by 1.5 cm. The left auricular endocardium was smooth and the right ventricle somewhat dilated. The valves were normal. The coronary arteries showed minimal intimal atherosclerosis, with no evidence of luminal obstruction. The endocardium was somewhat opaque and appeared thickened in areas. The aorta was smooth and elastic. The right lung weighed 570 Gm., left, 430 Gm.; both were edematous and congested on section. The tracheobronchial tree was clear. The liver weighed 1660 Gm. and on section had a "nutmeg appearance." The gall bladder and extra hepatic biliary tract were normal. The pancreas and spleen were grossly normal. The right kidney weighed 220 Gm., the left, 200 Gm. Neither kidney showed any gross lesions. The remainder of the genitourinary tract was normal. The adrenals and thyroid were normal. A small area of intense engorgement was noted in the prepyloric region of the stomach. The remainder of the gastrointestinal tract was normal. The brain was not examined.

Microscopic Findings. A section through the apex of the left ventricle disclosed a large mural thrombus overlying a markedly thickened endocardium. There was beginning organization at the base, with capillary proliferation. There was fresh hemorrhage in the subendocardial areas. Sections through the

septum membranaceum, and through the left auricular endocardium, disclosed entrapment of the myoneural conduction tissue in the thickened endocardium. The lungs showed congestion, edema, and focal hemorrhages. Recent severe hemorrhagic central necrosis was manifest in the liver. The pancreas, spleen, kidneys, and remaining organs were not remarkable.

Discussion

In reviewing the literature on diseases of the mural or parietal endocardium, descriptions of hearts showing varying degrees of endocardial thickening under a variety of names and differing circumstances are frequently encountered. This change is sometimes the result of a diffuse fibroelastosis, such as is found in certain congenitally malformed hearts; at other times, the picture is simply one of moderate sclerosing edema and collagenization of the subendocardial space, as may be seen in some cases of widespread scleroderma; still another pattern may show endocardial fibrosis as one of reparative fibrosis associated with inflammation, infarction, or thrombosis. For example, endocardial thickening may follow primary coronary disease. Certain cases of subacute bacterial endocarditis may spread from the valves to involve the adjacent auricular and ventricular endocardium. Inefficient valves, with extensive regurgitation, may lead to endocardial scarring. Rheumatic and diphtheritic myocarditis may involve the mural endocardium and heal with scar formation. Weiss and others[1] described endocardial thickening in association with scleroderma. Schürmann and MacMahon[2] described similar changes in patients with malignant nephrosclerosis, thrombophlebitis, and periarteritis nodosa. Recently, we have had the opportunity to study the same lesion in a classic case of disseminated lupus erythematosus. Dock[3] has included endocardial thickening as a histologic component of the beriberi heart. In most, if not all, of these cases, this endocardial change has played little or no recognizable part in the clinical symptomatology of the systemic disease under discussion and the lesion has been but an incidental autopsy finding

In the two cases under consideration, the changes involving the endocardium dominated both the clinical picture and the autopsy findings. In brief, we recognize the possibility that this lesion may appear as a component of more complex clinical and anatomic syndromes, but we would like to emphasize that this condition alone may simulate coronary disease and that it may, as an isolated disease entity, lead to death.

Davies[4] described a great number of cases of endocardial fibrosis occurring in African natives, and his clinical and anatomic descriptions coincide strikingly with the lesions found in our two cases. His cases showed either endocardial necrosis with secondary thrombosis, or diffuse subendocardial sclerosis. Bedford and Konstam[5] reported 40 cases of unexplained heart failure in West African troops serving in the Middle East in whom subendocardial fibrosis was a prominent anatomic feature. Smith and Furth,[6] in 1943, published a report of three cases of fibrosis of the endocardium complicated by mural thrombosis; Gray[7] reported two similar cases in Europeans living in West Africa, and in a recent abstract, Dammin, Glaser and Roberts[8] called attention to this same type of lesion.

Clinical Features. Most patients suffering from this disease are young adults. In our cases the ages were 34 years (case 1), and 27 years (case 2). Other case reports list the ages of patients with this syndrome as: 15 years,[9] 23 years (2 cases)[10] and between 20 and 30 years.[5] In Davies'[4] series, death occurred most commonly in adolescence and early adulthood. Sex appears to be of little importance. These patients present clinically a rapid, weak pulse. In our second case the pulse rate was unobtainable at a stage during which the apical rate was 136. The blood pressure is low-normal, or occasionally unobtainable. Hypertension was not encountered in our cases, and other reports seem to agree with this observation. Rather marked disturbances of cardiac rhythm, including gallop, are common. The electrocardiogram is abnormal but not diagnostic. The course, if uncomplicated, is afebrile.

In case 1 slight temperature rises were noted which were explainable on the basis of a transient bronchopneumonia, pulmonary infarction, and thrombophlebitis. Clinically, the hearts, both by physical and x-ray examination, show enlargement usually to the left, bu

right-sided enlargement may also be seen. The findings on physical examination are those usually encountered in cases of myocardial failure and are related to the duration of the illness as well as to the extent of the pathology found at autopsy. Any bizarre manifestations of the diseased endocardium may be observed, including embolic accidents involving any of the viscera or extremities. Again, secondary thrombophlebitis following bed rest, with subsequent pulmonary embolism, may occur (case 1). The course of the disease is quite variable. Some patients may die in the first severe attack; others, unresponsive to all therapy, may survive less severe attacks only to succumb to repeated bouts of myocardial failure.

Present laboratory findings seem to be of little aid in the diagnosis. Davies[4] has found a transient eosinophilia in some of his cases, the cause of which is unknown. Both of Gray's[7] cases showed a high, but difficult to explain, eosinophilia. He stated, however, that both of his cases had *Loa loa* infestations, which could easily account for the eosinophilia. The probability of parasitic infestations in Davies'[4] cases cannot be overlooked. No eosinophilia was noted in either of our cases.

Pathologic Features. Microscopic examination of the endocardium in areas free of mural thrombi disclosed a very homogeneous, uniform type of subendocardial thickening consisting almost entirely of collagen. In some areas the collagen had the appearance of an eosinophilic ground substance, distinctly different from scar tissue. In other locations the collagen was fairly cellular and contained numerous spindly fibroblasts. This collagen had filled the subendocardial areas and caused a tremendous thickening of this layer. It had enveloped the myoneural tissue of the cardiac conduction system and spread along the vascular septa of the myocardium. In areas with overlying mural thrombus formation, the thrombi were perpetuated into the bays and along the endocardium of the trabeculae, producing a sequential thrombosis of the thebesian vein system at that site. Similar observations have been reported by Flynn and Mann.[11]

In areas of mural thrombus formation, it is practically impossible to differentiate endocardium, subendocardial connective tissue, and subendocardial myocardium. Nevertheless, in areas free of thrombi or adjacent to thrombi, this distinction is rather apparent and the involvement here is primarily in the subendocardial connective tissue. That the entire process is initiated from within out, that is, from endocardium to myocardium, is further attested to by the fact that the deeper myocardium is essentially free of primary disease. Bacterial stains failed to reveal the presence of any organisms in all of the areas examined. The inflammatory response appears to be entirely nonspecific, and in the healing process, there is a virtual absence of elastic tissue formation. This latter finding alone would seem to separate this entity from the fetal type of endocardial fibroelastosis described by Gross[12] and more recently, by Prior and Wyatt,[13] in which the elastic component is very conspicuous.

The sequence of events would appear to be as follows: First, there is an accumulation of a relatively cell-free fluid ground substance immediately beneath a swollen layer of endothelial cells which form the inner endocardium. This undergoes sclerosis and collagenization and may extend in between the adjacent muscle fibers. This basophilic material, now appearing as ground substance, may accumulate to such an extent that it may bulge above the level of the adjacent endocardium. It may constrict and even close the large venous sinuses reaching into the inner third of the myocardium. This change may be complicated by hemorrhage and recurrent thrombosis. One or all of these changes may recur so that older lesions, complicated by repair, organization, and pigmentation, may become increasingly complex and difficult to interpret. The underlying muscle, during the active phase of this process, can show atrophy, hydropic degeneration and necrosis.

The functional significance of this lesion depends on the type of reaction, its location, extent, and complications. In the two cases under discussion, the subendocardial tissues of the left ventricle were primarily involved. There was massive interventricular thrombosis, occlusion of venous sinuses, degeneration and necrosis of muscle fibers, and sclerosis of muscle bundles, all in the area in which the con-

duction system is most heavily concentrated. These findings could reasonably be correlated with the clinical symptoms and the electrocardiographic tracings.

The etiology of this disease is unknown. Even the nature of the lesion and its pathogenesis remain obscure. At best it seems to fall into the inflammatory group of diseases, dominated in its early stages by an exudation or accumulation of cell-free, protein-rich fluid into the subendothelial tissue spaces. In its later stages, sclerosis and collagenization of this intercellular ground substance is present. If there is hemorrhage or thrombosis, the pattern is complicated by organization and repair. The regressive changes, involving the underlying parenchymatous tissue which may play such an important functional role, would appear to be secondary and dependent upon the primary lesion in the interstitial spaces. There have been many hypotheses to explain the lesion, but none has been fully satisfying. One step, and possibly the first, would seem to be a change in the overlying endothelium, altering its permeability, and lowering the threshold of exchange between circulating blood and tissue fluids. Schürmann and MacMahon[2] postulated such an hypothesis to explain the vascular and parenchymatous lesions common to malignant nephrosclerosis, periarteritis nodosa, and scleroderma.

Summary

Two cases of a relatively obscure endomyocardial affection of unknown etiology have been presented. Each had a similar unresponsive clinical course manifested by chronic myocardial failure, and atypical clinical signs with negative cardiac histories. Each case had one common postmortem finding, characterized by a sclerosis and thrombosis of the parietal endocardium of the left ventricle. The coronary arteries and valve leaflets in each case were essentially healthy. It is recognized that endocardial sclerosis and even endocardial thrombosis may occur as a relatively incidental finding in some of the so-called collagenous diseases, but it is the purpose of this paper to point out the fact that this same lesion may occur to a remarkable degree in an isolated form and that it may lead to death. The fact that this condition appears in young adults, mainly below the age of 40, should serve as a stimulus to its further elucidation.

Sumario Español

Se discute una condición rara que generalmente ocurre en adultos jovenes y puede simular enfermedad de las coronarias. Los pacientes son afebriles, la presión arterial es baja, el pulso es débil ligero y con marcadas irregularidades en ritmo cardíaco. La condición no responde a tratamiento y los pacientes pueden sobrevivir ataques iniciales solo para sucumbir en una recaída. En las porciones del endocardio no envueltas por trombos murales hay espesamiento subendocardial colagenizado desprovisto de tejido elástico. La etiología es desconocida.

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The Ballistocardiogram in Mitral Stenosis

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The ballistocardiograms of 13 of 14 patients with "pure" mitral stenosis were found to show a characteristic late diastolic and early systolic deformity. The deformity consists of a footward wave which precedes the I wave, often resulting in "doubling" of the I, or fusion with the I, producing a wide, deformed wave. Ballistocardiograms of patients with mitral insufficiency did not consistently show this deformity. Immediately after commissurotomy this abnormality was diminished, but was not completely eliminated. Some possible factors concerned in the genesis of this pattern are discussed.

DESPITE the extensive application of the ballistocardiographic method to the study of various disorders of the cardiovascular system, little attention has been given to the findings in the presence of rheumatic mitral stenosis. In 1941, Starr[1] reported several cases of rheumatic heart disease, with emphasis placed upon the changing "size" and improved form of the record after the administration of digitalis. He did not comment on the characteristics of the pattern, but it is of interest to note that the illustrated records from these individuals did show a deformity of the I wave, at least to some extent. In 1948, when reviewing a large variety of cardiovascular disorders, Starr and Mayock found abnormal ballistocardiograms in 45 per cent of their cases of rheumatic heart disease.[2] One case of mitral stenosis and insufficiency, reported in detail, was said to show abnormally small I waves, and slurred or notched IJ segments. On the other hand, Brown and his co-workers[3] were impressed by the diastolic waves in cases of mitral stenosis. Thirty per cent were said to show tall L waves, and 30 per cent prominent N waves. These workers did not broaden their comments regarding ballistic form, except as related to arrhythmias or "significant . . . myocardial damage." The studies of Starr and of Brown and their co-workers were carried out on high-frequency bed ballistocardiographs.

Mathers and associates, utilizing a Nickerson-type low frequency bed, reported two cases of rheumatic heart disease.[4] Both had abnormal records, with "bowing" of the JK segment. Newman and his co-workers, likewise using a low-frequency instrument, recorded ballistocardiograms on dogs before and after the experimental induction of mitral insufficiency. No significant change in ballistic form was noted.[5]

In several publications related to the use of the direct-body ballistocardiographic pick-up, Dock and his co-workers[6, 7] have commented on the presence of prominent L waves in the records from patients with rheumatic carditis and "mitral valve disease."

It is the purpose of this report to describe findings in clinically "pure" mitral stenosis, before and after commissurotomy.

Methods and Materials

All studies were performed on a high-frequency (9 or 10 cycles per second when loaded with 150 pounds of dead weight) Starr-type bed ballistocardiograph. Frontal plane "vector" records were taken by means of a method previously described.[8] Electrocardiograms (lead II) and belt pneumograms (strain gage) were recorded simultaneously, and in many instances these were combined with apex cardiograms and phonocardiograms. The conditions under which these ballistocardiographic studies were performed, the methods of analysis, and normal standards on which comparisons are based have been reported elsewhere.[9]

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Fourteen patients with clinically "pure" mitral stenosis were studied. They were made available to us through the courtesy of Drs. E. Cowles Andrus and Alfred Blalock. All of them fulfilled the criteria previously reported from The Johns Hopkins Hospital for acceptability for commissurotomy.[10-12] Cases with clinically significant mitral insufficiency were excluded from this group. Their ages ranged from 22 to 54, with a mean of 35 years. Twelve of the 14 cases were females (86 per cent). Functional disability was graded on the basis of the New York Heart Association Criteria.[13] One case was considered class I, the others were class II or III. All were studied immediately prior to operation, and consequently maximal clinical improvement had been obtained through the usual means prior to this study. Minor evidences of congestive failure were present in several instances (elevated systemic venous pressure, slight hepatomegaly, basilar rales), but all patients were able to lie comfortably in the recumbent position for the period of this test.

Findings on physical examination were those of relatively pure mitral stenosis. Three of the 14 had evidence by x-ray of enlargement of the left ventricle, while in the remaining cases this chamber was considered normal. The left atrium and/or pulmonary artery was prominent in all cases. Pulmonary artery pressure, determined by cardiac catheterization or direct needle-puncture at the time of thoracotomy, was elevated in all instances in which the procedure was successful (11 of 14 cases). In five cases the electrocardiogram was interpreted as showing right ventricular "strain." In the remaining cases the electrocardiogram was considered normal.

For comparison, eight cases of clinically determined mitral insufficiency (with or without stenosis) were selected from the Cardiac Clinic. Age and general clinical disability were comparable. The diagnosis of mitral insufficiency was based on the presence of a loud apical systolic murmur, with or without a thrill, and left ventricular enlargement. Patients with evidence of other valvular lesions were excluded.

In order to secure a comparable control group, the mean values for 18 normal females in the fourth decade[9] were utilized. The group with mitral stenosis is not strictly comparable to the normal group, in that 2 of the 14 patients were males. In addition, ages are not entirely comparable, since although the average age of the group with mitral stenosis was 35 years, there were three individuals over 40, and three under 30 years.

Utilizing the electrocardiogram for timing, and measuring all intervals and durations of waves to the closest 0.01 second, the abnormal deflection and normal systolic waves were tabulated in each case.

Results

A. Ballistocardiographic Form in Mitral Stenosis

In accord with previous ballistocardiographic experiences, moderate variation in ballistic form was found from case to case. Despite the overall variability, one anomaly was strikingly consistent. In 13 of the 14 cases of mitral stenosis, a deformity of the late diastolic and early systolic portions of the complex was found. This is shown in the examples diagrammed in figure 1, and illustrated in figure 2. This abnormality consists of a presystolic headward wave, often broad and rounded, sometimes sharply inscribed and highly variable, which is followed by a much more consistent footward deflection which precedes the I, and follows the electrocardiographic Q by 0.10 second ($\pm$0.03 second). This footward wave, which is later than the normal G, deforms the H wave, decreasing its amplitude or totally eliminating it. The I wave is characteristically distorted, and its inscription delayed. The distortion of the I ranges from clearly defined "doubling," that is, with the interfering anomaly and normal I separately inscribed, to fusion of these two footward waves, with a wide slurred "I" resulting. There are gradations of all degrees between these extremes.

In this series of 14 cases of mitral stenosis the J wave was usually normal. In two instances, the total ballistocardiographic pattern was grossly deformed, and in these the J wave was variously and inconsistently distorted. Six cases showed rounding and slurring of the expiratory J, although inspiratory form was normal. In the remaining six cases the J was normal in both phases of respiration. The K was likewise usually normal, except for the two totally deformed records, although an occasional expiratory complex was characterized by distortion of K. In only one instance was an unusually prominent L wave seen.

Mid- and late diastolic deflections were neither consistent nor striking, except for the presystolic deformity previously described.

The frontal plane "vector" studies were of

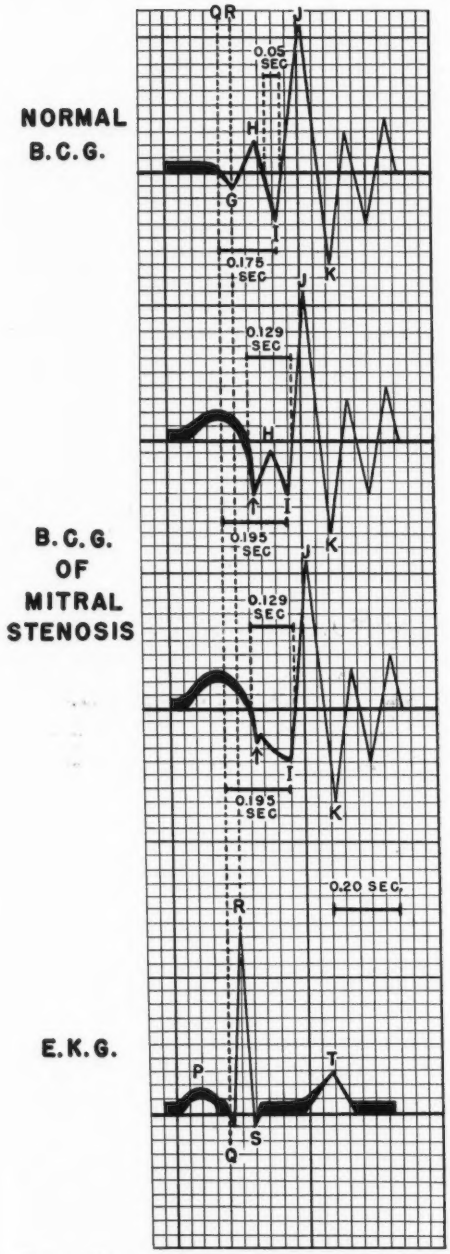

FIG. 1. Diagrammatic representation of the ballistocardiogram of patients with mitral stenosis. A normal ballistocardiogram is presented for comparison (above), an electrocardiogram for timing (below). Time lines represent 0.04 second. The diagrams illustrate complexes in which "doubling" of the I wave (second diagram), and "fusion" of the I with the early deflection (third diagram) occur. Note the abnormal footward deflection occurring 0.010 second after the electrocardiographic Q wave, and 0.06 second after the normal ballistocardiographic G wave. The I wave appears late (0.195 sec. after the Q) and its duration is quite prolonged. (See text for details.)

interest, since the distribution of the IJ loop differed from the normal. In normal adults the I is oriented footward and slightly to the right (as seen from the patient's head in dorsal recumbency), while the J is headward and slightly to the left.[8] In contrast to this pattern, the IJ axis in mitral stenosis is rotated slightly counterclockwise, that is, with the I oriented to the left and footward, the J to the right and headward. Fifty per cent of the records in this series revealed such a counterclockwise pattern, only one was clockwise, and the remainder were oriented along the head-foot axis. The vector distribution of the presystolic–early systolic deformity was clockwise in 10 of 13 cases. This was true especially with regard to the early footward wave, which tended to be oriented to the right of the head–foot axis, whereas the I was usually to the left. The result of this vector dissociation was that in several cases the deformity was much more striking, 60 degrees and 90 degrees clockwise from the head–foot axis, than in the conventional record, although clearly seen in the latter.

B. Quantitative Data in Mitral Stenosis

The complete quantitative data are summarized in table 1. The abnormal early footward deflection, which precedes the I wave, occurs an average of 0.097 second after the Q wave. If the one case with mitral stenosis in which this deformity did not occur is excluded, the mean interval from Q to this abnormal wave becomes 0.103 second. For contrast, this interval is compared statistically with the Q-G interval of normal controls (although this is not meant to imply that the origin of these deflections is similar). The mean Q-G in the controls is 0.044 second and the upper limit for this figure is 0.06 second. One record in

the mitral stenotic group was found to have an interval of 0.06 second while all others exceeded this figure. Measurements of the Q-G and Q-I were performed with the assumption that the first headward deflection after the "interfering" footward wave is the H, and the subsequent footward deflection the I.

figures are used, the mean Q-H interval is 0.153, which is 0.041 second longer than the mean Q-H interval in the control group. The mean Q-I is 0.195 second, or 0.020 second longer than in the normal females. These differences are statistically significant.

Of the remaining figures, only one was found

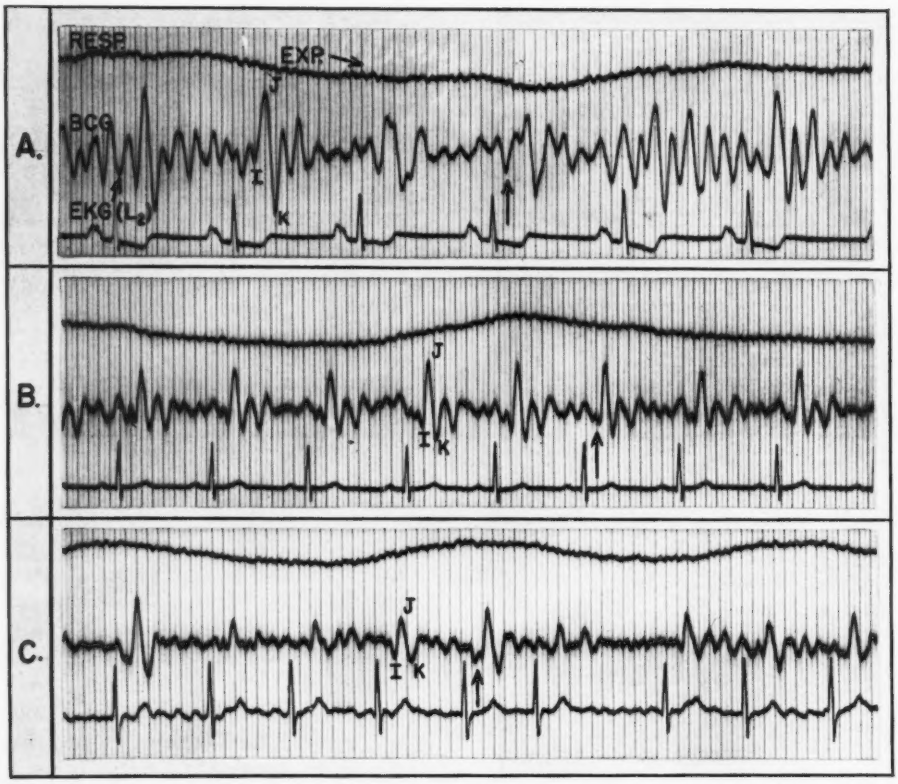

FIG. 2. Representative samples of the ballistocardiograms of patients with mitral stenosis. The arrows identify the abnormal footward deflections distorting the early portion of the systolic complexes. *A* shows an extreme example of the phasic shift in deformity of the ballistic complex with respiration. In *B* this phasic influence is not apparent, although consistently doubled and deformed I waves are present. In *C* is shown the record from a patient with atrial fibrillation in which the characteristic deformity is present.

Since this portion of the ballistocardiogram was distorted, the designation H and I may not be strictly applicable. Since 13 of 14 records were found to show the characteristic deformity, mean values were obtained for the total group, and also for the 13 patients in whom this finding was present. If the latter

to show a significant difference between the mitral group and the controls. This figure is the I wave duration. In measuring this interval, both the early interfering wave and the normal I wave were included, since they were often fused or so nearly fused that the "H" wave failed to reach the baseline. There is highly

significant difference between the normal (0.055 second) and the mitral stenotic I duration (0.1231 second).

In order to attempt correlation between clinical functional status, pulmonary arterial pressure, and the ballistocardiographic form, these findings were charted. Clinical disability is graded into classes 1 to 4 (New York State Heart Association); the pulmonary arterial pressures are the average of several readings in millimeters Hg; the electrocardiogram is charted as showing a normal pattern or right ventricular strain. The ballistocardiographic pattern is classified 1 to 4, with class 1 representing an intermittently deformed early systolic component, class 2 a consistently present deformity, with separately inscribed waves ("doubled" I), class 3, "fused" I, that is, the fusion of the interfering deflection and the I, and class 4, gross abnormality, with deformity not only of early systolic but also of the J and K.

TABLE 1.—*Quantitative data from 14 cases of mitral stenosis, with 18 normal females of the fourth decade as controls. Values exceeding 2.00 in the last column represent statistical significance (i.e., d/S.E. = 2.0).*

Value Analyzed	Mitral Stenosis (mean)	Normal Control (mean)	Difference of Means	Diff./ S.E.
Q-to abnormal footward wave	0.097	(Q-G) 0.044	0.053	5.88
Q-H	0.146	0.112	0.034	3.18
Q-I	0.191	0.175	0.016	1.88
Q-J	0.249	0.245	0.004	0.45
Q-K	0.343	0.334	0.009	0.37
I duration (mean)	0.123	0.055	0.068	9.58
J duration (mean)	0.102	0.101	0.001	0.30
IJ Amplitude (mean)	12.04	12.90	0.90	0.68
Ra (IJ exp./IJ in sp. × 100)	62.36	68.40	6.04	1.17

As is apparent from table 2, there is a general, but not entirely consistent, tendency for those individuals with increasing degrees of clinical disability and higher pulmonary artery pressure to show more marked ballistocardiographic abnormality.

Of the small group of eight patients with clinical mitral insufficiency, only one had a record which could have been considered compatible with the mitral stenotic pattern. Four cases showed an intermittently "doubled" I wave, but without the widening and delayed inscription present in mitral stenosis. The mean Q-I interval in the patients with mitral insufficiency is 0.173 second, which is not significantly different from that in the controls. The I is widened, being 0.076 second, but is significantly less than the 0.123 second duration found in the ballistocardiogram in mitral stenosis.

TABLE 2.—*Tabulation of clinical features and degree of abnormality of the ballistocardiogram. (See text for explanation of ballistocardiogram grading system.) Note the general trend to increasing abnormality with increasing clinical disability and rising pulmonary artery pressure.*

Patient	Functional Clinical Disability (Class 1–4)	Pulmonary Artery Pressure	Electrocardiographic Right Ventricular Strain	Ballistocardiographic Abnormality (Class 1–4)
N. B.	Class 1	?	absent	Class 1
M. B.	Class 2	?	absent	Class 1
A. B.	Class 2	?	absent	Class 1
E. J.	Class 2	49/27	absent	Class 2
R. J.	Class 2	51/22	absent	Normal
M. C.	Class 2	54/24	present	Class 2
J. W.	Class 2	55/37	?	Class 4
P. B.	Class 2	60/30	absent	Class 3
F. G.	Class 2	85/51	present	Class 4
M. H.	Class 3	40/22	absent	Class 2
G. B.	Class 3	50/43	absent	Class 4
L. E.	Class 3	82/47	present	Class 3
J. A.	Class 3	91/56	present	Class 3
E. C.	Class 3	138/57	present	Class 3

Postoperative ballistocardiograms were obtained in six cases, but unfortunately all were performed shortly after operation, and it is probable that at least six months will be required before optimal improvement is attained, following commissurotomy. All six cases showed satisfactory results immediately after operation. In general, the postoperative ballistocardiographic changes were not striking. Four cases showed some improvement, and in five the ballistic amplitude increased. The early deformity persisted to some degree in all cases although it was distinctly less prominent in

four. Figure 3 illustrates the most striking case, with an abnormal preoperative record. and an almost normal one following operation. The early systolic deformity is far less evident.

Discussion

In the ballistocardiograms of many normal individuals there is a footward wave which precedes the I wave. This normal early deflection has been designated the "G" wave, and occurs simultaneous with or within 0.06 second after the electrocardiographic Q wave (0.06 second represents the upper limit for the mean Q-G interval, not for isolated complexes). This deflection shows phasic variation with respiration.

The ballistocardiogram in 13 of 14 cases of mitral stenosis has been shown to be characterized by an abnormal early systolic wave. In contrast to the normal G, this footward deflection occurs late (mean of 0.103 second after the Q) and is associated with a late I wave (mean Q-I 0.195 second).

The deformity seems to represent an abnormal footward impact, which occurs either in late diastole or early systole, distorting the early systolic portion of the ballistic complex, and producing a "doubled" I wave. When the deformity is further advanced, fusion of this deflection with the I occurs, producing a wide rounded I (mean I duration 0.129 second). This has not been observed in normal individuals. It has been seen in other disorders, especially constrictive pericarditis[14] and aortic or iliac thrombosis.[15]

The presence of a "splintered" or "doubled" I wave has been noted by several observers with the vertical ballistocardiograph.[2, 16, 17] The second wave has been called I_2, by Krahl, who demonstrated that this impact varies in position during the respiratory cycle, occurring early in expiration, late in inspiration.[16] A similar, though less definite respiratory influence is present in some cases of mitral stenosis. Starr has stated that his studies with the vertical ballistocardiographic technic demonstrated no significant differences in the timing or the duration of waves from the results with the horizontal instrument.[17] Krahl suggests that the early wave, which occurs with the

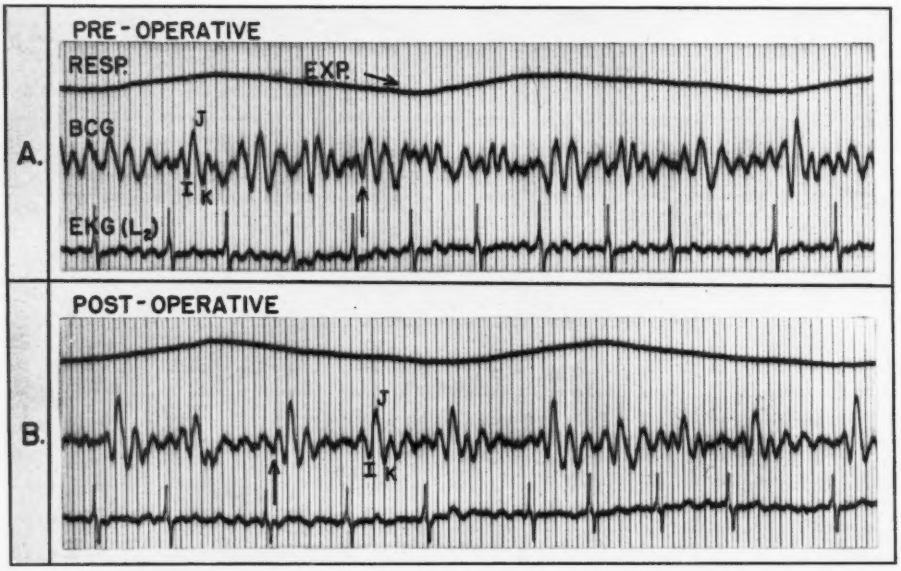

Fig. 3. The ballistocardiogram of a patient with mitral stenosis before and three months after commissurotomy. There is obvious improvement in ballistic form, with lessening of the early systolic deformity (arrows identify the abnormal footward wave).

vertical ballistocardiograph in normal persons, may be the result of deceleration of the blood ejected by the right ventricle, as it meets the pulmonary arch or peripheral pulmonary resistance. If such a factor were responsible, then by analogy one could postulate that the profound increase in pulmonary artery resistance and reduced elasticity in mitral stenosis accentuate this deceleration impact to a far more striking degree, and that this factor contributes to the development of the above described anomaly even on the horizontal bed.

Kuo and associates[18] reported three cases in which "double peaked" systolic complexes were present. One of these was an individual with mitral stenosis. All showed two headward waves preceding the J wave, which would result in "doubling" of the I. These workers demonstrated the presence of ventricular asynchrony in all three cases, and suggested that this deformity occurs when pulmonary ejection precedes aortic, and is maximal in the presence of right ventricular hypertrophy. There is right ventricular hypertrophy in a large percentage of cases of mitral stenosis, but the significance of the asynchrony factor remains to be determined. Kuo and co-workers[18] observed "two upward deflections" in two cases of mitral insufficiency as well.

The possible contribution of an intracardiac impact as an alternative or additional factor must be considered when attempting an explanation of the deformity found in mitral stenosis. The high pressure in the pulmonary circuit and left atrium and the normal or low left ventricular pressure suggest, on theoretical grounds at least, that an abnormal late diastolic–early systolic impact could develop during ventricular filling. It is clear that atrial systole is not a necessary requirement, since the deformity described occurs in the presence of atrial fibrillation as well as with normal sinus rhythm.

Thus the explanation for the delayed, widened, and deformed early systolic ballistocardiographic complex is not immediately forthcoming. Whether the increased pulmonary resistance, ventricular asynchrony, or atrioventricular pressure gradient contribute significantly, either individually or collectively, cannot be determined from the available data. Other factors may well be responsible.

It is clear, however, that in 13 of 14 cases of relatively pure mitral stenosis, a distinct, though not specific, deformity is present. Whether the presence of this pattern will be of value in differentiating individuals with stenosis from those with significant mitral insufficiency remains to be determined. This small series would suggest that if the fully developed pattern (class 3 or 4) described previously is present, the lesion is predominately stenotic, but larger groups of patients with both lesions are required before real significance can be attached to this finding.

Immediate postoperative results suggest that the deformity is lessened, though not eliminated by commissurotomy. Prolonged observation of the patients constituting this series will be necessary before final conclusions may be drawn with respect to changes in the ballistocardiogram following successful commissurotomy. It will also be of interest to determine in what degree long-term clinical improvement is reflected by ballistocardiographic improvement.

Summary

1. The ballistocardiographic findings in 14 individuals with "pure" mitral stenosis have been reported. Thirteen of the 14 were shown to have a consistent deformity of the early systolic portion of the ballistic complex.

2. Six cases were studied following satisfactory commissurotomy. The abnormal early systolic pattern was lessened, but not eliminated, in four.

3. The possible contributions of increased pulmonary vascular resistance, right ventricular hypertrophy, ventricular asynchrony, and abnormal atrioventricular pressure gradient are discussed.

4. The presence of a relatively consistent ballistic deformity in mitral stenosis is at the present time a physiologic, ballistocardiographic challenge, more than a finding with definite clinical usefulness.

Sumario Español

Los balistocardiogramas de 13 de 14 pacientes con estenosis mitral pura mostraron

una deformidad característica tarde en diástole y temprano en sístole. La deformidad consiste en una ondulación caudal que precede la ondulación I, a menudo resultando en una doble I, o fusión con la I, produciendo una ondulación deforme. Balistocardiogramas de pacientes con insuficiencia mitral no mostraron esta deformidad consistentemente. Inmediatamente después de comisurotomía esta abnormalidad dismisnuyó, pero no fué completamente eliminada. Algunos factores que posiblemente conciernen con el origen de esta abnormalidad se discuten.

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Management of Shock in Acute Myocardial Infarction

By ABRAHAM GOOTNICK, M.D., AND FREDERICK H. KNOX, JR., M.D.

Shock complicating acute myocardial infarction contributes materially to the over-all mortality. The wisdom of combating the shock has been a matter of dispute, many clinicians holding that the fall in blood pressure has the salutary effect of reducing the work of an acutely injured heart. This report deals with a four-year experience in active intervention for shock. The data suggest that timely intervention for shock is frequently life-saving, and may be instrumental in halving the mortality of the sickest patients.

THE ARGUMENTS for and against vigorous blood replacement in cases of bleeding peptic ulcer have had their counterpart in the question how best to treat shock associated with myocardial infarction. In the ulcer controversy, misgivings have been voiced lest restoration of normal blood pressure "blow off the clot" and undo the salutary homeostatic effects of a fall in blood pressure; similarly, in the management of myocardial infarction, the fall in blood pressure is regarded by many as an adaptive mechanism for reducing the load on an acutely injured myocardium. Current teaching, as reflected in texts on diseases of the heart, yields no clear answer to the question: Should the shock of acute myocardial infarction be treated or let alone? White,[1] in his chapter on myocardial infarction, does not mention the treatment of shock. Friedberg,[2] states: "Therapeutic measures ordinarily employed in other forms of shock may be dangerous, lest they overload the circulation, or strain the injured heart muscle." Of several widely used textbooks of medicine only one includes in the treatment of acute myocardial infarction a section on management of shock, and advocates the use of vasopressor drugs and blood or plasma.[3] Stroud states[4]: ". . . perhaps a drop in blood pressure is an effort on the body's part to protect the myocardium." Gilbert states[5]: ". . . I see no necessity for giving plasma or for transfusion. There are contraindications to the use of peripheral vasoconstrictor drugs. Blood pressure should be left where it is and not tinkered with."

The issue has been clouded by inadequate definition of terms. A fall in blood pressure of some degree occurs in the large majority of cases of myocardial infarction. In most of these, the drop in blood pressure occurs at onset or shortly thereafter, is of moderate degree, associated with only minor indications of vascular collapse, and (most important) is transitory, with spontaneous recovery in the direction of normal blood pressure within minutes or an hour or two. Experience with patients whose blood pressure behaves in this way has been very favorable and has served as a deterrent against intervention for shock. In contrast, there are other patients whose fall in blood pressure is of marked degree, who show the full-blown picture of shock and who remain in this state for many hours with a steadily deteriorating circulation until death. The gravity of this type of shock is attested to by every observer who has studied a large number of patients with acute myocardial infarction. A fall in systolic blood pressure below 90 mm. Hg, or of the pulse pressure below 25 mm. Hg places the patient in a category in which recovery is uncommon.[6, 7] The experience may be summarized in the conclusion of Master and his co-workers[8]:

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"When the blood pressure fell below 80, the patient usually died."

Although there are numerous recorded observations on the level of blood pressure in myocardial infarction, and on the prognostic implications of various degrees of hypotension, references to duration of shock are few and less explicit. It has been our observation that *duration* of shock is the more important prognostic criterion. When profound circulatory failure persists for a number of hours, recovery is extremely rare. This is understandable in the light of Wiggers' experimental studies on hemorrhagic and postreinfusion shock.[9] When, after prolonged posthemorrhagic hypotension, blood is reinfused, the animal rallies only temporarily; ". . . slow spontaneous circulatory failure and eventually death follow. Irreversibility develops during the period of prolonged hypotension . . . myocardial depression is indicated by a subminimal stroke volume when venous pressures are elevated to normal levels. . . ." Other experimental studies on shock show that myocardial lesions were consistently found in dogs who survived longer than eight hours.[10] Clinically, moreover, the effect of protracted shock on the coronary circulation has long been recognized, notably in the report of Blumgart and co-workers.[11]

Early studies by Fishberg, Hitzig and King presented evidence to show that the circulatory failure associated with acute myocardial infarction is not an entity separate from other varieties of shock, and that in common with other types of shock it is characterized by marked decrease in venous return, diminished circulating volume, and lowered venous pressure.[12] Later, Stead and Ebert observed in patients with myocardial infarction simultaneous diminution of peripheral blood flow and congestion of the pulmonary or systemic circulation They concluded that this combination of events was a reflection of primary failure of the heart rather than curtailment of venous return characteristic of other varieties of shock.[13] The controversial role of reflex factors in the circulatory collapse, and the probability that abrupt diminution in cardiac output may well be the significant initial event, do not affect the central consideration: Prolonged critical lowering of aortic pressure subjects an already injured myocardium to greatly diminished perfusion with blood. The well established relationship of extensive myocardial necrosis to severe lasting shock has reconciled physicians to the view that such degrees of myocardial injury are incompatible with life, and that exertions against drastic shock are not likely, therefore, to alter a fatal outcome. Nevertheless, it cannot be that mere massiveness of the infarction foredooms a patient; there are patients who have survived a third and fourth authenticated myocardial infarction and who eventually come to autopsy showing that they had lived on with remarkably little intact myocardium. The problem, therefore, is tiding the patient over the acute functional derangement of the circulation precipitated by the myocardial injury.

In our experience with acute myocardial infarction during the years 1948 to 1951, we found 32 instances of acute myocardial infarction marked by severe and prolonged shock, who were treated actively with one or another combination of plasma, blood and a vasopressor drug. For purposes of this study, we have eliminated cases of shock who were treated but in whom there was significant possibility of spontaneous recovery. Those excluded from this study were patients who exhibited no more than moderate clinical manifestations of circulatory collapse, or whose pulse pressure did not fall below 25 mm. Hg; those who, though definitely in shock, were in circumstances which permitted prompt treatment and reversal of the shock; and those whose shock, of whatever duration, was quickly responsive to initial therapeutic measures. We have included only patients whose shock was so profound at the beginning of treatment as to justify no expectation of survival. The data in table 1, and the representative case abstracts which follow, are intended to make clear our basis of selection. This is a group of patients in whom from previous experience we should have expected a mortality close to 100 per cent.

For vasopressor effect we depended on drugs which raise blood pressure without accelerating the heart, namely Paredrine, Neosynephrine

TABLE 1.—*Clinical Findings, Treatment Used and Results in 32 Cases of Severe Shock Following Myocardial Infarction*

Name, Age & Diagnosis	Hours In Shock Before Treatment	Clinical Manifestations	Total Hours Treatment of Shock	Treatment and Effects	Remarks
D. E., w. m., 58.	2	Fall of B.P. from 100/80 to 0* with onset of ventricular tachycardia. In coma; incontinent.	26	Sinus rhythm after 1.5 Gm. Pronestyl; shock persisted. After 6 hours of treatment with Neosynephrine and plasma B.P. 92/75; patient improved. Recurrence of ventricular tachycardia and shock. No further response. Total Neosynephrine 80 mg. Total plasma 1500 cc.	Died
G. J. B., w. m., 74; one previous myocardial infarction.	4	Moribund on admission, B.P. not perceptible.	1	300 cc. of plasma; 28 mg. of Neosynephrine. No response.	Died 1 hour after admission.
G. J. K., w. m., 55; one previous myocardial infarction.	25	B.P. and pulse not perceptible; deep cyanosis; coma.	2	Plasma 550 cc. Neosynephrine 48 mg. No response. Dead in two hours.	Old and fresh infarctions at autopsy.
C. H., Negro male, 54.	2	Fall in B.P. from 150/120 to 80/40. Profuse cold sweat, cyanosis, Cheyne-Stokes respiration.	27	Fluctuating B.P. with rise up to 110/80 after each dose of Neosynephrine. Pulmonary edema cleared as B.P. rose. Plasma 1250 cc. Neosynephrine 139 mg.	B.P. on discharge 110/80.
C. A. J., w. m., 55.	1	Fall in B.P. from 170/110 to 0. Severe chest pain, vomiting, cyanosis.	23	1000 cc. of 10% glucose sol. 500 cc. blood. Total Neosynephrine 108 mg. Moderate pulmonary edema cleared with emergence from shock.	Recovered.
T. A. E., w. m., 61.	Unknown	Cyanotic, covered with cold sweat, pulmonary edema.	3	Pulmonary edema cleared after I.V. morphine. Highest systolic B.P. 60 mm. Hg. Remained in shock until death. Total Neosynephrine 43 mg. No blood or plasma.	Autopsy: Large area of myocardial necrosis and pericardial hemmorhage.
B. T. E., w. m., 52; two previous strokes.	2	Fall in B.P. from 190/110 to 0; severe pulmonary edema.	2	35 mg. of Neosynephrine ineffective. Remained in shock until death.	Shock precipitated by third cerebrovascular accident.
F. J. Q., w. m., 81; two previous infarctions.	5	In coma, incontinent, clammy, cyanotic. Systolic B.P. 50 mm. Hg by palpation.	11	Plasma 750 cc., Neosynephrine 68 mg. Highest B.P. reached 80/65. Remained in shock.	Died
L. G., w. m., 54; one previous infarction.	2	B.P. 0, cold, cyanotic, vomiting. Increasing pulmonary edema on second day of shock.	26	Plasma 500 cc., blood 500 cc. in first 12 hours. Out of shock after 16 hrs., but required Neosynephrine for 10 hrs. more. Total 92 mg.	Discharged Symptom-free with B.P. 115/70.
S. A. L., w. m., 53.	29	Cyanotic, stuporous, incontinent. B.P. 70/60.	2	Plasma 450 cc. Neosynephrine 28 mg. No response.	Autopsy: Infarction of entire septum and most of anterior wall.

TABLE 1.—*Continued*

Name, Age & Diagnosis	Hours in Shock Before Treatment	Clinical Manifestations	Total Hours Treatment of Shock	Treatment and Effects	Remarks
L. A. A., w. m., 61; one previous infarction.	5	Fall in B.P. from 190/110 to 0. Pulmonary edema, stuporous.	1½	Initial response to Neosynephrine; B.P. up to 90/70 and pulmonary edema cleared. Chest pain recurred, B.P. fell to 0, with pulmonary edema. No response thereafter. Neosynephrine 25 mg.	Autopsy: Old posterior infarction & fresh extensive anterior infarction.
W. W. R., w. m., 63; one previous infarction.	48; severe shock 6 hrs.	B.P. 70/60, cold, clammy, cyanotic, in marked congestive failure.	14	Initial improvement with rise in B.P. to 80/50. Severe shock thereafter. Plasma 1000 cc. Neosynephrine 63 mg.	Autopsy: Old posterior, fresh anterior infarction.
R. J. F., w. m., 51.	6	Stuporous, clammy, cyanotic, vomiting. B.P. 0.	48	B.P. 92/60 after 5 hrs. of treatment but shock recurred when Neosynephrine withheld. After 48 hrs. patient alert, warm, voiding. B.P. 102/54. Plasma 1000 cc. Neosynephrine 105 mg.	Initial response to drug alone inadequate; effect of adding plasma dramatic.
Readmission: one previous infarction.	1½	B.P. 0. Deep cyanosis, coma, incontinent.	20½	Prompt response to first dose of Neosynephrine. Neosynephrine 102 mg. Plasma 750 cc.	Recovered.
P. S., w.m., 74; one previous infarction.	½	Markedly cyanotic, cold and wet, vomiting, Cheyne-Stokes breathing. Systolic B.P. 50 mm. Hg.	4½	Transient response with peak of B.P. 110/95. Thereafter unresponsive. Plasma 500 cc. Neosynephrine 27 mg.	Autopsy: Old posterior and fresh anterior infarctions; bronchial tree filled with aspirated gastric content.
R. J. H., w. m., 60; two previous myocardial infarcts.	25	B.P. 0, cold, in coma.	4½	Systolic B.P. reached 60 mm. Hg. briefly. Never out of shock. Plasma 750 cc. Neosynephrine 29 mg.	Autopsy: Two previous infarctions, one fresh infarction.
P. T. B., w. m., 48.	½	Bilateral bronchopneumonia, marked cyanosis, rapid, shallow respirations, B.P. 80/68.	24	B.P. rose to 88/72, 94/72. Antibiotics, anticogulants, Neosynephrine 44 mg. No I.V. fluids. Improvement interrupted by cerebrovascular accident.	Autopsy: Extensive anterolateral infarction; cerebral thrombosis.
H. J. M., w. m., 47; one previous infarction.	2	Ventricular tachycardia and fall of B.P. to 0., Cold sweat, vomiting, cyanotic.	32	Sinus rhythm restored with quinidine promptly but B.P. still 90/80. After Neosynephrine, B.P. 104/86. Dependence on drug continued 32 hrs. Plasma 1250 cc. Neosynephrine 108 gm.	Recovered.
C. J. J., w. m., 51; one previous infarction.	24	B.P. 84/50. In marked pulmonary edema, cyanotic, stuporous.	6	Initial response, B.P. to 98/64 and clearing of pulmonary edema. Later, recurrence of intractable pulmonary edema and death. Neosynephrine 25 mg., no I.V. fluids.	Autopsy: Previous anterior and fresh posterior infarctions. Marked pulmonary edema.

TABLE 1.—*Continued*

Name, Age & Diagnosis	Hours in Shock Before Treatment	Clinical Manifestations	Total Hours Treatment of Shock	Treatment and Effects	Remarks
G. C. M., w. m., 56; one previous infarction.	9	Moribund; B.P. 0	8½	Plasma 500 cc. Blood 500 cc. Neosynephrine 42 mg. No response.	Died
G. A. C., w. m., 70; one previous infarction.	5	Stuporous, clammy, cyanotic, vomiting. Fall in B.P. from 210/120 to 60/?.	22	B.P. rose to 80/64, fell again between doses of Neosynephrine. Slow emergence from shock. Plasma 500 cc. Blood 750 cc. Neosynephrine 69 mg.	Discharged with B.P. 124/90.
W. A. F., w. m., 51.	3	In pulmonary edema, heart rate 112, B.P. 0.	15	B.P. rose to 96/72. Pulmonary edema cleared. Blood 750 cc. Neosynephrine 48 mg.	Discharged symptom-free with B.P. 96/70.
M. D. F., w. m., 55.	4	Cold and sweating, cyanotic. B.P. 78/50.	44	Intermittent rise in B.P. to 90/62 after Neosynephrine. Blood 500 cc. Plasma 1000 cc. Neosynephrine 98 mg.	B.P. on discharge 108/68.
B. A. W., w. m., 53; one previous infarction.	3	B.P. 150/110 to 76/60. Severe mid-chest pain, unrelieved for 36 hrs. by repeated doses of morphine.	32	Blood 500 cc. Plasma 1000 cc. Neosynephrine 60 mg. Slow emergence from shock.	Recovered.
A. B. J., w. m., 60; one previous infarction.	3	Cold, cyanotic, in coma, incontinent, B.P. 60/?.	15	First rise in B.P. to 80/50 only after plasma started. Blood 500 cc. Plasma 500 cc. Neosynephrine 38 mg.	B.P. on discharge 120/80.
M. R., w. m., 60; two previous infarctions.	29	B.P. 65/50. Cold, wet, anuric, vomiting.	7	Plasma 1500 cc. Neosynephrine 52 mg. No response.	Died
W. E. M., w. m.,56; two previous infarctions.	5	Vomiting, oliguric, deeply cyanotic, B.P. 70/50.	19	Fluctuating B.P. first 12 hours. hours. Out of shock when B.P. remained at 95/70. Plasma 1000 cc. Blood 500 cc. Neosynephrine 70 mg.	Recovered.
W. E. O., w. m., 60; one previous infarction.	1	B.P. 0. vomiting, cyanotic and cold, stuporous.	16½	Highest B.P. reached 90/80. No clinical improvement. Plasma 1000 cc. Blood 500 cc.	Autopsy: Old posterior and fresh anterior infarctions.
A. B. J., w. m., 61; three previous infarctions.	½	B.P. 65/55, profuse cold sweat, cyanotic, vomiting.	14½	B.P. rose to 80/60 then fell to 0. Increasing pulmonary edema till death. Plasma 500 cc. Neosynephrine 48 mg.	Died
R. J. B., w. m., 42; one previous infarction.	8	Coma, marked cyanosis, respirations 8 per minute, B.P. 0.	10½	B.P. to 65/?, briefly to 88/?. Emerged from coma, then relapsed. Coramine. Neosynephrine 62 mg. Plasma 1000 cc.	Autopsy: Old myocardial infarction and extensive fresh infarction.
S. G., w. m., 62.	3	Fall in B.P. from 200/140 to systolic of 100 by palpation. Cyanosis, intractable hiccup, marked pulmonary edema.	19	Digitalized. No I.V. fluids. Intermittent response to Neosynephrine till blood pressure reached 130/80. Pulmonary edema cleared thereafter. Neosynephrine 48 mg.	Discharged with B.P. 170/90.

TABLE 1.—*Concluded*

Name, Age & Diagnosis	Hours In Shock Before Treatment	Clinical Manifestations	Total Hours Treatment of Shock	Treatment and Effects	Remarks
G. H. I., w. m., 70; one previous infarction.	5	Cyanotic, cold and clammy, stuporous, vomiting. Fall in B.P. from 210/120 to 0.	22	Transitory rise in B.P. to 80/64, 74/58. Out of shock when B.P. reached 110/84. Blood 750 cc. Neosynephrine 72 mg.	Discharged with B.P. 124/90.
W. A. F., w. m., 51; one previous infarction.	3	Severe pulmonary edema. B.P. 0.	15	Pulmonary edema cleared following Morphine and Neosynephrine. Remained in shock until blood was added. Neosynephrine 46 mg. Blood 750 cc.	Recovered.

Oxygen and Demerol or morphine were received by all patients and are not referred to in the table. Most patients received anticoagulants, but in the majority the shock occurred too early in the course of the illness for this treatment to be relevant.

Digitalis was administered to the following patients: R. J. F. (second admission), L. G., C. J. J., S. G., G. J. K., B. T. E. and W. W. R.

The following received mercurial diuretics: R. J. F. (second admission), H. J. M., A. B. J., and W. W. R.

Most patients received some 5 per cent or 10 per cent glucose solution. Only C. A. J. received an effective quantity.

* B.P. imperceptible.

and norepinephrine. However, none of the patients treated with Paredrine was sufficiently in shock to qualify for inclusion in this study. The patients treated with norepinephrine are the subjects of a separate investigation to be reported in the future. The present group, therefore, were all treated with Neosynephrine, administered intravenously or intramuscularly, in doses varying from 2 mg. to 7 mg., and at intervals of 15 minutes to an hour. The size of the dose, route of administration, and intervals between doses were determined by the initial status of the patient, the presence or absence of sufficient circulation to absorb the drug from the tissues, and adequate or inadequate response to previous doses of the drug. Plasma or whole blood was infused in quantities varying from 250 cc. to 1500 cc. Only outright pulmonary edema complicating the shock was considered a contraindication to the use of blood or plasma.

Treatment in other respects was that accorded to most patients with myocardial infarction. Morphine or Demerol was given in doses sufficient to control pain. All patients included in this study received oxygen, either in a tent or by nasal catheter. Some of the patients, whose course was marked by increasing pulmonary congestion, received a mercurial diuretic, and several were digitalized. With the exception of those who presented a decisive contraindication, all received adequately controlled anticoagulant therapy.

CASE ABSTRACTS

R. J. F. was a 51 year old white man who had collapsed abruptly and was found three hours later barely conscious and complaining of agonizing anterior midchest pain. When brought to the hospital six and one-half hours after onset, the patient appeared moribund. Heart rate was 40 and regular; blood pressure could not be determined; temperature was 96.6 F. The heart sounds were barely audible. The patient was cyanotic and semistuporous; his skin was covered with perspiration and cold. He had received no medication prior to admission. The electrocardiogram showed a pattern typical of acute posterior wall infarction.

The patient was placed in an oxygen text. An infusion of 5 per cent glucose in water was started at once and replaced by plasma within 15 minutes. Five milligrams of Neosynephrine were administered intravenously and another 5 mg. intramuscularly. Fifty milligrams of Demerol were given subcutaneously. Within an hour his blood pressure was 60/40. Repeated 5 mg. doses of Neosynephrine were given intravenously at intervals varying from 20 to 40 minutes until the blood pressure rose to 86/72.

At the end of five hours of treatment, in the course of which 55 mg. of Neosynephrine and 1000 cc. of plasma had been administered, the blood pressure was 92/60. the skin was less cyanotic, he was conscious and no longer in pain. Treatment with Neosynephrine and plasma was discontinued. An hour later he was again covered with cold perspiration, blue, and blood pressure had dropped to 88/72. Neosynephrine was resumed and the blood pressure again rose to 96/66 within 15 minutes of the first 5 mg. dose. Thereafter, the drug was continued in 3 mg. to 5 mg. doses at progressively lengthening intervals for a total of 48 hours. At the end of this time the patient's blood pressure was 102/54, the first time systolic pressure had exceeded 100 mm. Hg. One thousand cubic centimeters of plasma was administered, all of it within the first five hours after admission. The total quantity of Neosynephrine given was 105 mg.

Five weeks after admission anticoagulant therapy had been discontinued and the patient was discharged, symptom-free, with a blood pressure averaging 105/70.

Six months after his first myocardial infarction, this patient was admitted a second time approximately 12 hours following onset of severe chest pain. The patient was in coma, cold and blue, pulseless, and exhibiting Cheyne-Stokes respiration. Blood pressure was unobtainable. Heart sounds were faintly audible, regular, approximately 140 per minute. The electrocardiogram showed a pattern of acute anterolateral infarction.

The patient was placed in an oxygen tent, 7 mg. of Neosynephrine were administered intravenously and an infusion of 5 per cent glucose in water was started. Plasma was substituted for the glucose solution 10 minutes later. Within 30 minutes blood pressure was 86/74. Neosynephrine was again given, 5 mg. intravenously and 5 mg. intramuscularly, and 5 mg. doses of the drug were repeated at intervals averaging one-half hour. In the course of the succeeding 12 hours, blood pressure readings were 86/74, 80/62, 88/70, and 90/74. On two occasions, the systolic blood pressure remained above 90 mm. Hg for 90 minutes before dropping again. The patient's color improved gradually and periodic breathing became regular. He regained consciousness 12 hours after admission and complained of anterior mid-chest pain; this was controllable with 10 mg. of morphine sulfate given subcutaneously. The blood pressure at this time was 102/75. During this 12 hour period he had received 102 mg. of Neosynephrine and 750 cc. of plasma.

The patient's course from this point on was marked by steadily increasing pulmonary congestion which was controlled with some difficulty by the use of mercurial diuretics, augmented later by digitalis. Eventually, he was free of congestive failure on a regimen including low-sodium diet, maintenance doses of digitalis, and a weekly dose of a mercurial diuretic. Blood pressure at the time of discharge was 100/76.

C. A. J., a 55 year old white male known to be hypertensive, was admitted with complaints of epigastric and midchest pain of seven days' duration, associated with much eructation of gas, anorexia and abdominal distention. Acute myocardial injury was suspected and confirmed by an electrocardiogram which showed the pattern of posterior infarction. Treatment, including anticoagulant therapy, was begun. During the succeeding five days the patient complained of intermittent pain of considerable severity in the anterior chest. Low-grade fever continued, and the blood pressure which had been 170/100 on admission, now averaged 120/85.

On the morning of the sixth hospital day, the patient was seized with severe retrosternal pain, was nauseated and vomited once. Within an hour, blood pressure had become imperceptible, heart sounds were feeble, and heart rate was 140 and regular. The patient had become ashen-gray; profuse, cold perspiration covered the entire body; he was restless and markedly apprehensive. He was placed in an oxygen tent and 10 mg. of morphine sulfate were given intravenously. A slow drip of 10 per cent glucose in water was started and a first dose of 5 mg. of Neosynephrine was given intravenously. Additional 5 mg. doses of Neoynephrine were given before a systolic blood pressure level of approximately 70 mm. Hg. could be detected by palpation. An electrocardiogram taken at this point, two and one-half hours after onset of the acute pain, showed changes consistent with fresh extension of the myocardial infarction. The patient remained conscious, but was cyanosed, cold, vomited repeatedly, and was clearly in deep shock. During the succeeding 10 hours, 1000 cc. of 5 per cent glucose in water, given intravenously, 500 cc. of whole blood, and repeated intravenous doses of Neosynephrine had the effect of maintaining a blood pressure averaging 70/50. Several observers who left notes on the patient's chart unanimously considered his prognosis hopeless.

Rales could now be heard over the lung bases which had been clear initially, but there was no overt pulmonary edema. Treatment continued with only repeated doses of Neosynephrine; intravenous fluids were omitted. Intermittent peaks of systolic blood pressure were recorded at 88, 94 and 92 mm. Hg, shortly after a dose of Neosynephrine, but these levels were not sustained. During the next 12 hours the patient very slowly emerged from shock. The blood pressure rose to 95 systolic and finally, 24 hours after onset of his circulatory collapse, blood pressure was 110/90 and the patient was out of shock. A total of 108 mg. of Neosynephrine had been administered. Serial electrocardiograms were characteristic of fresh extension of the posterior myocardial infarction, showing reappearance of positive S-T

deviation in leads which previously had shown only the T-wave changes of a healing injury.

C. H., a 54 year old Negro, had been a known hypertensive for eight years. The background included a stroke six years previously and an intermittently active duodenal ulcer first diagnosed four years previously. The patient had been on maintenance doses of digitalis for congestive failure which had begun one and one-half years prior to admission. The day before admission, the patient was seized with severe pain in the left chest radiating from the left axilla to midsternum. With this there was marked exacerbation of his dyspnea, and great weakness. Physical examination 24 hours after onset of the pain showed an acutely ill, dyspneic, heavily perspiring Negro male. Blood pressure was 150/120, temperature 99, respiration 24; heart rate was 90 and regular. No signs of pulmonary or visceral congestion were evident, and the only other notable finding was old right hemiplegia. Electrocardiogram showed a typical pattern of acute posterior infarction and an occasional ventricular premature contraction.

On the third night after the infarction, following an initially favorable course, the patient grew increasingly dyspneic, had recurrence of chest pain, and perspired profusely. When seen two hours later, his blood pressure had fallen to 80/40 and he was in pulmonary edema. The patient was placed in an oxygen tent, a single 10 mg. dose of morphine sulfate was given intravenously and Neosynephrine was given in repeated 5 mg. doses intravenously at 15 to 20 minute intervals. The blood pressure rose intermittently in response to the drug, and the pulmonary edema cleared within an hour. Blood pressure thereafter fluctuated between 76/56 and 100/70, with one briefly sustained peak of 160/110. Twenty-four hours after onset of the shock the patient was still in a state of circulatory collapse, cyanotic, bathed in clammy perspiration and showed Cheyne-Stokes breathing. The pulmonary edema had not recurred. His blood pressure was sustained at the levels indicated but lapsed within one-half hour after each intravenous dose of Neosynephrine. A slow infusion of plasma was started and from this point on effectiveness of Neosynephrine was much more lasting. Twenty-nine hours after onset of shock, following a total of 139 mg. of Neosynephrine and 1250 cc. of plasma, the patient was warm, voiding, breathing easily, and able to take food. Blood pressure was 106/80 and remained stable without further medication.

Careful study failed to reveal evidence of a fresh cerebrovascular accident, of bleeding from his ulcer or any other source, or of any extracardiac reason for the shock. The patient was discharged with a blood pressure of 110/80 and did not thereafter regain hypertensive levels. Two years later a follow-up examination showed a blood pressure 140/90.

G. J. K. was a 55 year old white man whose past history included diabetes mellitus of eight years' duration and a myocardial infarction one year previously. He was on a diabetic regimen which included neutral-protamin Hegedorn insulin, 40 units daily, and he took a daily maintenance dose of Digoxin. Five days prior to admission he was seized with severe retrosternal pain, became very weak and vomited. The pain recurred intermittently thereafter, and on the day of admission the pain grew much worse and it was associated with great weakness and dyspnea. On admission blood pressure was 120/80, the heart was moderately enlarged and a grade II systolic murmur was heard over the entire precordium. The only other finding of note was moderate dependent edema of the lower extremities. The electrocardiogram showed a pattern of recent extensive anterior infarction, superimposed on a previous posterior infarction.

The patient's course was uneventful until two weeks after onset of his infarction, when he again complained of severe chest pain. He developed a protodiastolic gallop rhythm, and the electrocardiogram showed changes consistent with extension of the myocardial injury. The patient was weak and vomited repeatedly. The skin was cyanotic and clammy. Blood pressure was 106/90. Despite the marked deterioration of the patient, antishock therapy was withheld, apparently because the systolic blood pressure exceeded 100 mm. of Hg. A check of the blood sugar showed no hypoglycemia. The following morning, 24 hours after his abrupt change for the worse, the patient was moribund. He was stuporous, cold, without perceptible pulse or blood pressure, and was blue despite the administration of oxygen. Plasma and intravenous Neosynephrine were administered but with no effect, and the patient died after two hours of intensive treatment which included 48 mg. of Neosynephrine and 550 cc. of plasma.

Autopsy confirmed the electrocardiographic interpretation of an old posterior and extensive acute anterior myocardial infarction.

P. S., a senile, incoherent, 74 year old white man, was admitted seven days after the onset of severe chest pain. He had vomited repeatedly following the onset of his pain. Except for moderate dyspnea the patient was not in distress at the time of admission. Significant physical findings included rales over the left chest posteriorly and faint heart sounds. Blood pressure was 110/80; temperature 100.2 F. and respirations 24. Electrocardiogram showed complete atrioventricular block, a ventricular rate of 55 and a pattern of recent extensive anterior infarction.

Twelve hours after admission the patient went into shock abruptly. Blood pressure fell to 80/60, he became stuporous, and developed Cheyne-Stokes respiration. Rales and rhonchi were audible over both lung bases posteriorly. Repeated intravenous

doses of Neosynephrine and 500 cc. of plasma resulted in an intermittent rise in blood pressure to 90/70 and at one point to 110/95, but the patient remained cyanotic, stuporous and incontinent. He received 500 cc. of plasma and 27 mg. of Neosynephrine but failed to rally and died five hours after lapsing into shock. At autopsy, an old posterior infarction and an extensive anterior infarction were found. The entire bronchial system on the left was filled with aspirated gastric contents, and there were many areas of pulmonary atelectasis.

H. J. M., a 47 year old white man, was admitted two weeks after onset of severe mid-chest pain, diagnosed at another hospital as acute anterior myocardial infarction. Electrocardiograms were in keeping with this diagnosis. The patient was asymptomatic on admission, presented no significant abnormalities on physical examination, and did well on a regimen of restricted activity and anticoagulant therapy. During the fourth week in hospital, increasing dyspnea developed, the heart rose to 120 per minute, the liver became enlarged and tender, and congestive changes were detectable in the bases of the lungs. Response to a mercurial diuretic was satisfactory. The blood pressure was 105/85. Despite the absence of pain, the reappearance of leukocytosis, of low grade fever, and characteristic S-T segment changes in the precordial leads led to the diagnosis of fresh infarction six weeks after the initial one. The following day the patient was seized with severe chest pain which responded to a single 10 mg. dose of morphine. His course for a week thereafter was uneventful, and serial electrocardiograms showed the expected evolution of an acute anterior myocardial infarction. On the eighth day after onset of the fresh infarction, the patient vomited his breakfast and complained of sudden weakness. Ventricular tachycardia at a rate of 190 was found. This responded readily to a total dose of 2 Gm. of quinidine sulfate, but the patient soon lapsed into deep shock. He had reverted to sinus rhythm, and the heart rate varied between 100 and 120. The blood pressure, which had been 105/75, was now imperceptible. Repeated 5 mg. doses of Neosynephrine intravenously and intramuscularly, and 500 cc. of plasma resulted in a rise of blood pressure to 90/80, but 18 hours after onset the patient was still in marked circulatory collapse, cyanotic, oliguric, exhibiting Cheyne-Stokes respiration and increasing pulmonary congestion. Prognosis at this point was considered practically hopeless. Within the next six hours, he gradually improved on a regimen of plasma and Neosynephrine, the lung cleared progressively, his color became normal, he stopped vomiting and began to void. Blood pressure now was 104/86, 90/66. The total duration of shock was 34 hours. He had received a total of 108 mg. of Neosynephrine and 1250 cc. of plasma.

The patient had a slow convalescence, but finally did well and was returned to his sedentary job on a maintenance dosage of digitalis. The blood pressure on discharge was 125/80.

Results

The abstracted case histories presented are representative of the histories of the entire group of 32 patients. Fourteen of these 32 patients recovered from their shock, and 18 died.

The patients with myocardial infarction associated with severe shock were of the same age distribution as the entire group with acute myocardial infarctions. The average age of the 14 survivors was 55 years, of the 18 who died, 60 years. Only 11 of our 32 patients were undergoing their first myocardial infarction. Twenty had had one or two previous infarctions, and one had survived three well-documented previous infarctions. Of the 11 with shock complicating an initial infarction, two out of three survived the acute attack; of the 21 who had had previous infarctions, only one out of three survived the acute attack.

An important factor bearing on the outcome of shock therapy was the length of time the patient had remained in deep shock before treatment was instituted. None of our patients survived whose shock had lasted more than eight hours without treatment.

Half of those who failed to recover went into shock at the onset of the acute attack; the rest went into shock at a later time within the first eight days following infarction. Among the survivors, all but two developed shock after a delay of one or several days, so that most were already in the hospital and within reach of prompt intervention.

In the large majority (26 of 32 cases), shock was precipitated by the myocardial infarction proper. In these 26 patients, there was no manifestation of complicating thromboembolic developments, of acute blood loss, of infection, or of significant change in the cardiac mechanism. In two, shock was precipitated by ventricular tachycardia. In one of these two the shock persisted for many hours after the rhythm had reverted to normal; he emerged from shock after 34 hours. In the other, ventricular tachycardia could not be controlled and this patient's shock persisted until death.

Only two developed shock from thromboembolic complications; a stroke in one patient who had had two strokes previously, and multiple cerebral and renal infarctions in another. One patient went into shock from hemopericardium and tamponade, and one from massive pulmonary atelectasis and infection.

In all 32 patients, evidence of acute myocardial infarction was unequivocal electrocardiographically, and in the 15 patients who came to autopsy the predicted infarctions, recent and old, were found without exception.

The use of Neosynephrine was not associated with detectable alteration of the cardiac mechanism. In those patients whose infarction was manifested by premature contractions or runs of ectopic rhythm, or by altered atrioventricular conduction, the addition of Neosynephrine to the regimen appeared to have no effect on the duration or severity of the disturbance. In only one patient with initially regular sinus rhythm did several supraventricular premature contractions appear in the course of Neosynephrine therapy; however, these premature contractions disappeared within 15 minutes despite continued administration of the drug, and it was felt that Neosynephrine was not the cause.

Except for terminal unresponsiveness in the patients who died, the vasopressor effect of Neosynephrine persisted with repeated doses given over the course of many hours. However, neither the drug alone nor intravenous infusion alone, whether of blood or plasma, was as effective as the two used together. It was repeatedly observed that plasma intravenously might fail to raise the blood pressure appreciably until followed by Neosynephrine. In the same patient, when the blood pressure had again fallen, the pressor effect of a dose of Neosynephrine alone might be negligible but would be augmented noticeably when followed by blood or plasma.

We were unable to detect any differences between the effects of plasma and whole blood. In several cases hematocrit determinations were made, and these were uniformly above normal. The significant advantage of plasma was its prompt availability, without the time lag involved in typing and cross matching blood.

Survival occurred, in some of our patients, after a remarkably long period of profound circulatory collapse. It was not unusual for a patient who had been in deep shock for a number of hours, and moribund on admission, to respond to treatment partially, and then continue, barely alive, at a blood pressure level of perhaps 80/65, for 24 or 36 hours. One required 48 hours of treatment before definitely emerging from shock. The effect of shock treatment in these patients was made evident in many instances by the repeated fall of blood pressure to imperceptible levels shortly after an infusion of blood or plasma had ended or when a dose of Neosynephrine was too long withheld. Among those who died, the majority showed no response at all to treatment, lapsed into progressively severe shock and died in a short time. Several, however, responded partially and lived many hours in a state of shock before they died. We have come to regard patients with acute myocardial infarction, however severe their shock, as having a chance for life. The chance is less the longer they have been in shock before treatment is begun, and it improves progressively the longer they remain alive under treatment.

Pulmonary edema complicating the shock occurred in 11 patients, and of these four survived. This combination is a particularly unfavorable one. For one thing, it reflects myocardial injury of extreme severity. For another, much of the therapy directed against pulmonary edema is intended to reduce venous return to the pulmonary circulation, and whatever reduces venous return reduces cardiac output also, and aggravates the shock. The number of patients treated is obviously too small for final conclusions, but our experience suggests that in choosing between the two coexisting problems it is more rewarding to place emphasis on combating the shock. The four survivors received no therapy directed toward the pulmonary edema other than small doses of morphine. They showed impressive clearing of the lungs as the blood pressure rose and they emerged from shock. In other instances tourniquets to the extremities, oxygen

by pressure mask, and rapid digitalization failed to influence the pulmonary edema favorably. The patients remained in shock and died in a short time. None of the patients in this group were among those we have treated with ethyl alcohol inhalation.[14] Added to the favorable results we have observed with this method is the theoretical consideration that the improvement in respiratory function is not bought at the price of reduction in venous return.

Repeatedly, we encountered the sequence of severe shock leading to pulmonary edema as the terminal event. It would appear that pulmonary edema in such cases may not be simply a matter of "backward failure" but a late effect, reflexly induced, of extreme myocardial and cerebral anoxia. The favorable effect of correcting shock on the pulmonary edema suggests that the decisive factor is increased perfusion of the coronary and cerebral circulations.

The relationship of blood pressure levels to clinical status was only crudely consistent. While it is true that generally a patient whose systolic blood pressure rose to 100 mm. Hg could be expected to recover, there were exceptions in whom a systolic blood pressure of 100 mm. Hg or slightly higher was recorded while all the clinical manifestations of critical shock continued and the patient went on to die. The pulse pressure was more consistently accurate as an index of the circulatory status of the patient. A patient emerging from shock, with warm extremities, improving color, and functioning kidneys, might have a blood pressure of 85/50 when another, deep in shock, might show a blood pressure of 95/80. Clinical recovery from circulatory failure in all those who survived was associated with attainment of a pulse pressure of at least 25 mm. Hg.

Comment

This experience with 32 instances of severe shock complicating myocardial infarction is notable more for the 14 who survived than for the 18 who did not. As may be seen from the examples described, the subjects of this study were the kind who contribute a substantial segment of the total mortality in any large series of acute myocardial infarctions. If one patient with hemopericardium and the 74 year old patient with massive aspiration of gastric contents are excluded as having been beyond help, our results would indicate that active intervention for shock offers the hope of reducing by half fatalities from this complication.

Of the 32 patients, 26 went into lasting shock without any detectable reason other than the effects of acute myocardial infarction. However meticulous the preventive measures against thromboembolism, rhythm disturbances, pulmonary infection and other complications, the adverse course of these patients could not have been forestalled. Their survival depended on sustaining a minimal circulation compatible with life during a critical period, until such hearts as were capable of recovery resumed adequate function. The contribution of shock therapy in these patients would seem to be prevention or limitation of progressive myocardial deterioration from the effects of shock, per se.

The adverse experience with patients who have been long in shock before treatment is begun suggests that it may be beneficial not to defer shock therapy until circulatory failure is manifest and well established. In the hope of encroaching further on the mortality from acute myocardial infarction, we have extended the use of vasopressor drugs, and also of blood or plasma where pulmonary edema did not threaten, to patients whose overt manifestations of shock are minimal or absent, but whose blood pressure falls from normal or hypertensive levels to a systolic level under 100 mm. Hg or to a pulse pressure under 25 mm. Hg. We find these patients much more promptly responsive than the critically ill group which is the subject of the present study; however, an undetermined proportion of these patients would be expected to recover spontaneously. How many are saved by prompt treatment from progressive and fatal shock it may be possible to evaluate eventually from analysis of a large and statistically valid experience.

Review of our records brings to light the great importance of systematic and well re-

hearsed teamwork in the management of the desperately ill patient in shock. A nurse cannot be given responsibility for the many decisions required by the fluctuating balance of the patient. The emergency situation requires a hospital environment. It may last for 48 hours or longer and require the close attention of a succession of resident physicians. A single experience of seeing a hopelessly shocked, moribund patient respond and later walk out of the hospital is generally sufficient to inspire physicians and nurses with the high morale and persistence necessary for the management of this type of emergency.

Summary

Acute myocardial infarction accompanied by deep and lasting shock was encountered in 32 patients in a three-year period. Fourteen of the 32 survived following vigorous management of the shock with vasopressor drugs, blood and plasma.

Shock, per se, contributes materially to the mortality from acute myocardial infarction. Active intervention against shock may spare the injured heart a period of greatly reduced coronary blood flow and appears to improve the chances for survival.

Sumario Español

El "shock" complicando infartos agudos del miocardio contribuye materialmente al total de la mortalidad. El raciocinio de combatir el shock ha sido discutible, muchos clínicos opinando que la caída en presión arterial tiene un efecto saludable al reducir el trabajo de un corazón agudamente averiado. Este informe relata la experiencia de cuatro años en la intervención activa en el shock. Los datos sugieren que la intervención temprana en el shock es frecuentemente una salvadora de vidas, y puede ser instrumental en disminuir la mortalidad de la mitad de los pacientes más graves.

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Effectiveness of Nupercaine Hydrochloride and Phenobarbital Sodium in the Suppression of Ventricular Tachycardia Associated with Acute Myocardial Infarction

By Abdo Bisteni, M.D. and A. Sidney Harris, Ph.D.

In 22 dogs with ventricular tachycardia accompanying myocardial infarction, Nupercaine hydrochloride was found to be a potent suppressor of ectopic impulses. When used alone Nupercaine also produced vomiting and convulsive movements. When combined with morphine, vomiting was eliminated, but convulsions still occurred. When combined with phenobarbital sodium or pentobarbital sodium, the ectopic impulse suppressor action of Nupercaine was enhanced and both vomiting and convulsive movements were prevented. The duration of ectopic impulse suppressor action was significantly greater in the phenobarbital-Nupercaine experiments than in any other group. No deaths occurred.

THE DEMONSTRATION by Mautz in 1936[1] that procaine, Metycaine and cocaine, locally applied, significantly increase the electrical threshold of heart muscle for premature systoles was followed by the widespread application of procaine as a protective agent in cardiac surgery. The studies of Mautz also initiated investigations designed to test the effectiveness of procaine in the prevention or suppression of cardiac arrhythmias of other origins. The experimental arrhythmias usually were produced in animals by the administration of epinephrine after sensitization with chloroform or cyclopropane. Some authors reported that procaine was effective in preventing ventricular tachycardia and fibrillation which commonly resulted from these procedures,[2-5] but Huggins and co-workers[6] found that the effects of procaine were too fleeting to be of practical value.[5] Zapata-Diaz and co-workers[7] terminated auricular paroxysmal tachycardia and ventricular premature systoles in a few cases by intravenous procaine, but failed in other cases of auricular paroxysmal tachycardia, auricular fibrillation, and ventricular tachycardia.

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Recently, procaine amide (Pronestyl), which is removed from the blood slowly, and which therefore has a prolonged duration of action, has been found more effective in preventing epinephrine-induced arrhythmias in animals and in the treatment of certain types of arrhythmias in patients.[8, 9] Procaine amide has been only partially successful in the prophylaxis and therapy of cardiac arrhythmias during thoracic surgery[10] and in the treatment of supraventricular arrhythmias.[11] It has produced distressing toxic reactions including paroxysms of ventricular tachycardia.[11]

The development of a standard technic for producing ventricular tachycardias associated with myocardial infarction in dogs has provided an experimental preparation which reproduces in many important features this grave type of arrhythmia in man.[12-14] A high frequency ectopic ventricular tachycardia produced by myocardial infarction often has been found difficult to control with drugs most commonly used clinically for this purpose,[13, 14] therefore the use of such an experimental preparation provides a severe test for the drug being studied. In tests of this kind, procaine proved to be practically useless. Procaine amide was effective in reducing high frequency tachycardias to safely low frequencies, but it would not stop all ectopic activity. Furthermore, it was quite ineffective in certain

other animals with lower frequency tachycardias and scattered ectopic ventricular complexes.[15]

The effectiveness of procaine amide, though leaving much to be desired, proved that drugs in the local anesthetic group could be of practical value in the suppression of high frequency ectopic rhythms resulting from cardiac pathology. Since only procaine and procaine amide of this series of chemically related compounds had been tested with animal preparations of this kind, it appeared important that the studies be extended to other drugs of the cocaine-like group. Nupercaine hydrochloride* was chosen for testing in a new series of experiments because of its high potency as a local and spinal anesthetic, and its long duration of action.

Technics

Myocardial infarction was produced in 22 dogs, and toxicity tests were made in two additional unoperated dogs. For surgery the animals were anesthetized with pentobarbital sodium, 30 mg. per kilogram. Using artificial respiration and aseptic surgical methods, the heart was exposed via an incision in the fourth intercostal space. The anterior descending artery was dissected free from adjacent structures just enough to allow the passage of ligatures at the level of the free edge of the left auricular appendage. The artery was occluded in two stages. The first ligature was tied snugly but not tightly around the artery together with a 20 gauge hypodermic needle, and the needle was withdrawn immediately. After 30 minutes of partial occlusion the second ligature was tied tightly, producing a complete and permanent occlusion. The wound was closed, and the dog was given careful postoperative attention, including fluids and morphine if needed.

On the morning of the following day, 16 to 24 hours after occlusion, a ventricular tachycardia with only slight variations in frequency from hour to hour was present in almost all animals. After four or five control electrocardiograms were recorded, testing was begun.

In the first four experiments Nupercaine† was administered by intravenous injection, 0.5 to 2.0 mg. per kilogram being diluted to 10 or 20 cc. with Locke's solution and injected via a plastic catheter during a period of 10 or 20 minutes. In the remaining 18 animals the Nupercaine was administered by constant venoclysis from a 50 cc. burette for periods from one to four and one-half hours at a rate of 50 cc. of fluid in 30 minutes. The fluid was Locke's solution containing Nupercaine in concentrations of 1 to 2 mg. per kilogram (weight of dog) per 50 cc. In a majority of experiments the concentration was 1 mg. per kilogram per 50 cc.

There were four groups of experiments: (*a*) animals that received Nupercaine alone; (*b*) Nupercaine after morphine, 3 or 5 mg. per kilogram; (*c*) Nupercaine after phenobarbital sodium, 25 or 40 mg. per kilogram; and (*d*) Nupercaine after pentobarbital sodium, 10 or 15 mg. per kilogram.

Blood pressure and the electrocardiogram were recorded simultaneously on a Sanborn Twin-Viso cardiette. A Statham gage and SIE Transducifier were employed in the pressure channel.

The arbitrary criterion of success which has been applied to tests with other drugs[14, 15] has been used in judging the results with Nupercaine. A successful test, according to the criterion is one in which the ectopic rate is reduced by the treatment to zero for some period of time, and maintained at a level less than one half of the pretreatment control rate for four hours or longer without toxic manifestations sufficiently severe to endanger the life of the animal. An effort was made to administer the minimal quantity of Nupercaine necessary to achieve this result.

Results

Nupercaine Alone

The intravenous administration of Nupercaine to four unanesthetized animals with ventricular tachycardia on the first day after occlusion and to 18 on the second day produced ectopic impulse suppressor action in every case. In all of the four first postocclusion-day tests and some of the second postocclusion-day tests with Nupercaine alone the reduction of frequency of ectopic complexes was accompanied by toxic reactions. The toxic manifestations were retching, vomiting, and convulsive movements. Retching and vomiting occurred in all first day tests with Nupercaine alone. Convulsive movements occurred in two of the four animals.

Figure 1, the chart of the first experiment with Nupercaine, illustrates both the ectopic suppressor action and the incidence of vomiting in a dog with a moderately high frequency ventricular tachycardia. More complete suppression of the arrhythmia undoubtedly could

* The Nupercaine hydrochloride used in these studies was generously supplied by Ciba Pharmaceutical Products, Inc.

† The shortened names Nupercaine, phenobarbital, and pentobarbital will be used in the remainder of the paper to mean Nupercaine hydrochloride, phenobarbital sodium, and pentobarbital sodium, respectively.

have been achieved if the rate of administration of the drug had not been slowed because of the vomiting. The doses and periods of administration are indicated in the figure. Nupercaine, 1 mg. per kilogram in 20 cc. of Locke's solution, was injected in 20 minutes at the times designated by 1, and 0.5 mg. per kilogram in 10 cc. Locke's solution was injected in 10 minutes at the times designated by 0.5.

According to the criterion of success, previously defined, all of the first postocclusion-day tests with Nupercaine alone could be classified as just barely successful. The ectopic frequencies could be maintained at levels about one half of the pretreatment ectopic rates or slightly less for periods up to four hours, but the toxic reactions were distressing. The

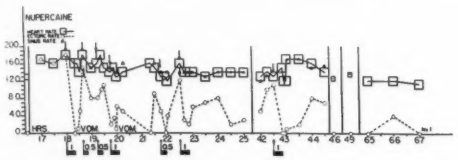

FIG. 1. Chart of effects of administration of Nupercaine to dog with ventricular tachycardia. Ordinate, frequency in beats per minute. Abscissa, hours after occlusion. Squares, total heart rate. Circles, ectopic rate, triangles, sinus rate. Doses described in text.

second postocclusion-day results will be further analyzed in succeeding sections.

Nupercaine Following Morphine

The effects of Nupercaine were tested following administration of morphine in five dogs with ventricular tachycardia. Four dogs received morphine, 5 mg. per kilogram, and one dog received 3 mg. per kilogram. The morphine was injected subcutaneously 30 to 75 minutes prior to the beginning of the administration of Nupercaine. Blood pressure was recorded during the main testing periods in all of these experiments.

Figure 2*A* is a chart of one of the experiments, and it may be regarded as portraying a typical result. During the control period, 19 to 20 hours after occlusion the ventricular ectopic rate was 190 to 210 per minute. After the beginning of the infusion of Nupercaine-Locke's solution the ectopic rate began to decline almost immediately, though it did not reach zero until 100 minutes later. At this time Nupercaine, 4.5 mg. per kilogram, had been infused. A total infusion of 9 mg. per kilogram was given during the first day. Tests in four of the five animals in this group fulfilled the criterion, but convulsive movements occurred in all of them. There was no vomiting.

Figure 2*B* illustrates the results of two infusions of Nupercaine in the same animal in which the test shown in 2*A* was made. This later test was performed without morphine on the second postocclusion day. It can be seen that vomiting occurred during the first infusion. Prompt and highly effective ectopic suppressor action was recorded during each infusion.

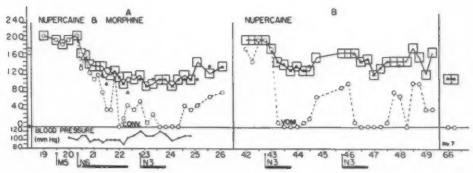

FIG. 2(*A*). Chart of experiment in which Nupercaine was infused after morphine, 5 mg. per kilogram subcutaneously. (*B*) Second postoperative day, Nupercaine without morphine.

In summary, morphine did not appreciably change the ectopic impulse suppressor action of Nupercaine, nor prevent convulsions. It did protect against nausea and vomiting.

Nupercaine after Phenobarbital

Nupercaine was administered to seven animals following sedation with phenobarbital, 25 mg. per kilogram and two dogs received 40 mg. per kilogram. The results in the tests with the different dosages of phenobarbital were similar except that the animals that received 40 mg. per kilogram slept more soundly during the tests and showed more residual effect on the following day. For these reasons the smaller dose of phenobarbital is regarded as preferable.

Figure 3 illustrates the effects of Nupercaine infusion following phenobarbital, 25 mg. per kilogram, to a dog with an ectopic ventricular tachycardia with a frequency of 210 to 220

per minute before the test. Infusion of Nupercaine, 4 mg. per kilogram in two hours, reduced the ectopic rate to zero. After this infusion had been finished for about one and one-half hours there was some return of ectopic activity. An additional infusion of Nupercaine, 3 mg. per kilogram, practically eliminated all ectopic beats for the remainder of the day. On the morning of the next day some ectopic activity had returned (rate 90 to 150). An infusion of Nupercaine, 2 mg. per kilogram, sufficed to restore a completely normal rhythm.

During this experiment, both days of testing, there was neither vomiting nor convulsive movements. In all of the eight experiments with Nupercaine after phenobarbital excellent control of the arrhythmia was achieved. There was no sign of nausea or

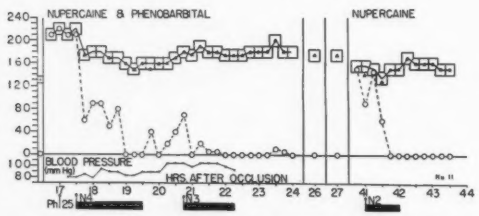

FIG. 3. Experiment in which Nupercaine infusion followed phenobarbital, 25 mg. per kilogram.

vomiting in any experiment, and only brief, doubtful, tonic extensor movement was noted in two animals. The ectopic activity was so well controlled that a much more stringent criterion than that adopted on a basis of experience with other ectopic suppressor drugs could have been fulfilled with 100 per cent success. The administration of Nupercaine on the second postocclusion day without additional phenobarbital to five of the dogs that had been treated on the first postocclusion day with phenobarbital and Nupercaine yielded good ectopic suppressor action without toxic manifestations. Phenobarbital, 25 mg. per kilogram, therefore exerts some protective effect for as long as 24 hours or more. From a therapeutic point of view the results are regarded as definitely superior to those in the experiments with Nupercaine alone or Nupercaine after morphine.

Nupercaine Following Pentobarbital

Nupercaine was administered to four dogs following sedation with pentobarbital sodium. In three dogs the dose of pentobarbital was 15 mg. and in the other one 10 mg. per kilogram. All of these dogs had high frequency tachycardias, the control rates in the different animals ranging from 200 to 310 per minute. Such tachycardias have usually been found more difficult to control than those with

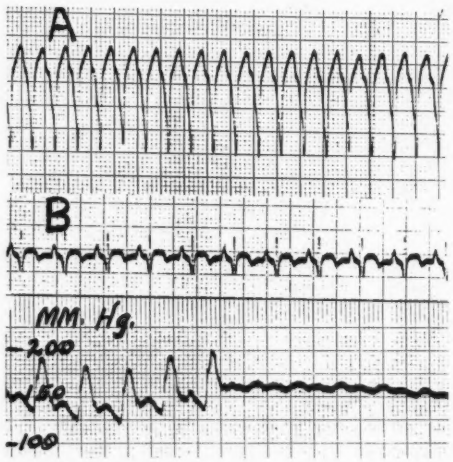

FIG. 4. Electrocardiograms from experiment in which Nupercaine infusion followed pentobarbital, 15 mg. per kilogram. (*A*) Control record before Nupercaine but after pentobarbital. (*B*) After infusion of Nupercaine, 1.5 mg. per kilogram in 45 minutes.

Lowest tracing is blood pressure recorded simultaneously with *B*. First part shows the arterial pulses. Systolic and diastolic pressures averaged about 185/135. Last part shows mean pressure record, average near 150.

lower frequencies. In the first postocclusion-day tests in all four of these dogs the ectopic rates were reduced to zero within a short time after the beginning of infusion of Nupercaine and good control was maintained over a period of four to six hours without toxic manifestations. The electrocardiograms in figure 4 are from the animal which exhibited the highest ectopic frequency prior to treatment in this series of experiments. The chart in figure 5 presents in detail the data from this experiment.

The record in figure 4*A* was taken just prior

to the beginning of the Nupercaine infusion. The ectopic rate at this time was 310 to 320. Figure 4*B*, made 45 minutes after the infusion was begun, shows complete restoration of sinus rhythm (fig. 5*A*, 19 hr. 45 min.). At this time Nupercaine, 1.5 mg. per kilogram, had been infused. To maintain good control throughout the day a total of 6 mg. per kilogram was administered.

On the following day (fig. 5*B*) Nupercaine was administered without the prior injection of pentobarbital and vomiting occurred repeatedly. In this second postoperative day test a total of 7 mg. per kilogram of Nupercaine was required to suppress the relatively mild tachycardia that had redeveloped overnight. The pentobarbital protection against toxic side reactions had disappeared.

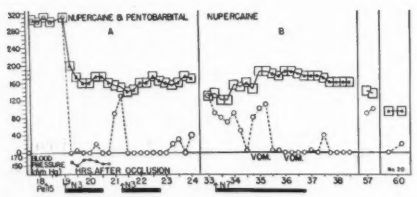

FIG. 5. Chart of experiment from which figure 4 was made. (*A*) First postocclusion day, Nupercaine after pentobarbital. (*B*) Second postocclusion day, Nupercaine alone.

The results in the other experiments with Nupercaine following pentobarbital sodium were similar to those represented by this experiment. Both barbiturates, phenobarbital sodium and pentobarbital sodium, increased the completeness of the ectopic impulse suppressor action of effective doses of Nupercaine, and counteracted the nausea and convulsive effects. The duration of the protection against Nupercaine toxic side reactions following phenobarbital is greater than that of the protection following pentobarbital.

Comparison of Durations of Ectopic Suppressor Effects of Just Adequate Total Doses of Nupercaine in the Four Groups of Experiments

The data on duration of control by the smallest quantities of Nupercaine which were found necessary to reduce the ectopic rate to zero and suppress the tendency of ectopic impulses to return for a period of four hours are summarized in table 1. The listed mean duration of control, 8.3 hours for phenobarbital-Nupercaine and about four hours for Nupercaine alone or in other combinations, do not show the full degree of superiority of phenobarbital and Nupercaine in this category. Only the hours of actually observed control were tabulated. In the phenobarbital-Nupercaine experiments suppression of ectopic activity exceeded the period of observations in every case. This was not true in the other three series.

TABLE 1.—*Summary of Data on Ectopic Suppressor Action and Toxicity of Nupercaine in the Four Series of First Postocclusion-Day Experiments*

Adjuvant drug	No. of dogs	Mean dosage*	Mean hrs. control†	S.D. (σ)	Toxic Signs		
					Vom.	Conv.	QRS‡
None	4	8.1	4.2	.06	4	2	1
Morphine	5	10	3.7	1.7	0	5	1
Phenobarb.	9	7.2	8.3	3.1	0	2§	1
Pentobarb.	4	6.2	4.6	1.35	0	0	0

Difference ÷ σ difference between the means of phenobarbital-Nupercaine and each of the other experimental groups indicates a probability greater than 99 to 1 that a real difference of means exists in the direction recorded; that is, the duration of suppressor action of phenobarbital-Nupercaine is greater than that of Nupercaine alone or in either of the other combinations.

* Total amount of Nupercaine, milligrams per kilogram, during the several hours of the test.

† Hours of control = hours during which ectopic frequency was maintained at less than ½ the pretest control rate.

‡ Duration of QRS greater than 150 per cent of control.

§ Mild stretching. Doubtfully included. No deaths occurred during or following tests in any of the above series.

Both series with barbiturates were superior to the other two in that toxic side reactions were almost totally eliminated by the barbiturates used. Morphine eliminated vomiting but not convulsions.

Toxicity Tests with Rapid Administration of Nupercaine in Unoperated Dogs

Two dogs without coronary occlusion were infused with Nupercaine at a rate of 8 mg. per

kilogram per hour, a rate four times as fast as that used in almost all of the dogs with ventricular tachycardia. These unoperated dogs received pentobarbital sodium, 15 mg. per kilogram, for sedation prior to the Nupercaine tests. With continuous infusion, these animals received Nupercaine, 24.5 and 22 mg. per kilogram, before the heart and circulation failed.

TABLE 2.—*Infusion of Nupercaine at a Rate of 8 mg. per Kilogram per hour. Electrocardiographic and Blood Pressure Effects. Sedation with Pentobarbital Sodium, 15 mg. per Kilogram*

Expt. No.	Nupercaine mg./Kg	Duration P-R	Duration QRS	Mean B.P.	Remarks
Nu 26	0	.08 sec.	.035 sec.	120	
	4	.08 sec.	.055 sec.	110	
	8	.14 sec.	.06 sec.	110	
	12	A-V dissoc.	.07 sec.	110	Irreg. nodal rhythm
	16	A-V dissoc.	.10 sec.	100	
	20	A-V dissoc.	.10 sec.	75	
	22	18 sec.*	.10 sec.	60	
	24	18 sec.*	.10 sec.	50	
	24.5		.18 sec.	10	Corneal reflex pres.
	25.0	Cardiac arrest		0	
Nu 27	0	.10 sec.	.035 sec.	125	
	4	.16 sec.	.14 sec.	135	
	8	.16 sec.	.16 sec.	115	Tonic convulsions
	12	.16 sec.	.16 sec.	105	Vent. extrasys. and conv.
	16	.18 sec.	.19–.11 sec.	100	Vent. extrasys. and conv.
	18	.19 sec.	.20 sec.	75	Intrav. block
	20		.18 sec.	35	Vent. extrasys. and conv.
	22		.16–.18 sec.	20–0	
		Cardiac arrest			

* Occasional association P-QRST

During the Nupercaine infusion electrocardiograms and blood pressures were recorded and the significant measurements are presented in table 2. At the fast rate of administration used significant prolongation of P-R and QRS intervals occurred after the animals received 4 to 8 mg. per kilogram. In animal 26, A-V dissociation began at 12 mg. per kilogram. In animal 27 A-V block and nodal rhythm began after 18 mg. per kilogram. The duration of QRS increased irregularly as the administration continued.

In animal 26 mean blood pressure decreased only from 120 to 100 with the administration of the first 16 mg. per kilogram of Nupercaine and was 75 mm. after 20 mg. per kilogram about 18 mg. per kilogram, and cardiac arrest occurred after 22 mg. per kilogram.

Electrocardiographic and Blood Pressure Observations during Slow Administration of Nupercaine in Tests upon Control of Ectopic Rhythms.

At the slower rates of administration used in the majority of tests of ectopic impulse suppressor action (2 mg. per kilogram per hour) only minor changes in the duration of P-R and QRS were observed. Data from two experiments are reproduced in table 3. The two experiments were chosen for publication because relatively large amounts of Nupercaine were used in them. The durations of P-R and of normally initiated QRS complexes could not be measured during the control period prior to the beginning of administration of

Nupercaine because no normal complexes existed. In experiment 22 after some normal cycles were restored by Nupercaine, 1 mg. per kilogram, the duration of P-R was 0.10 second and that of QRS was 0.05. At the end of the infusion of the total amount of Nupercaine required for control of the ectopic activity, 8 mg. per kilogram, P-R was 0.12 and QRS was 0.06 second. These small increases are only slightly greater than the range of spontaneous variations and are not indicative of dangerous effects. The data for experiment 17 show no prolongation of P-R and the increase in QRS is similar to that in experiment 22.

observed. Figure 6*B* illustrates one such episode. The onset of the broad complexes and pressure decline occurred after the infusion of Nupercaine, 7 mg. per kilogram at a rate of 4 mg. per kilogram per hour. Recovery of normal duration of QRS complexes and of mean blood pressure to a level higher than the control occurred promptly upon suspending the infusion (fig. 6*C*, 30 seconds after *B*).

No deaths occurred in the 22 dogs with ventricular tachycardia accompanying myocardial infarction during tests with Nupercaine alone or in combination with morphine, phenobarbital, or pentobarbital.

TABLE 3.—*Durations of P-R Intervals and of QRS Complexes in Dogs Undergoing Nupercaine Treatment for Ventricular Tachycardia. Rate of Nupercaine Infusion 2 mg. per Kilogram per Hour*

Hrs. after occ.	Rate		Nupercaine mg./Kg.	P-R sec.	QRS sec.	Mean BP mm.Hg
	Total	Ectopic				
Experiment 22 with Pentobarbital 10 mg. per Kilogram						
19 hrs.	175	80	1	0.10	0.05	120
19 hrs. 30 min.	180	10	2	0.10	0.05	145
20 hrs. 30 min.	185	0	4	0.11	0.05	160
21 hrs. 30 min.	170	0	6	0.11	0.055	160
22 hrs. 30 min.	155	5	8	0.12	0.06	140
Experiment 17 with Phenobarbital 25 mg./Kg.						
20 hrs. 15 min.	180	110	1	0.09	0.05	90
21 hrs. 15 min.	180	40	3	0.10	0.06	95
22 hrs. 15 min.	175	25	5	0.10	0.065	90
23 hrs. 15 min.	190	30	7	0.10	0.065	90
24 hrs. 15 min.	185	10–60*	9	0.095	0.06	85

* Forty-five minutes after the completion of the 9 mg. per kilogram, all complexes were normal. There was no return of ectopic activity.

Blood pressure tended to rise somewhat during a number of the tests, and to remain relatively unchanged in others. There was never a tendency toward a development of hypotension during slow administration of Nupercaine. The pressures listed in the two experiments in table 3 and those charted in figures 2*A*, 3 and 5*A* are illustrative of the series.

During some ventricular tachycardia tests in which Nupercaine administration was faster than usual, some brief periods of wide slurred QRS complexes (intraventricular block) accompanied by declining blood pressure were

DISCUSSION

The foregoing experiments have shown that Nupercaine and phenobarbital, used as described, constitute a relatively safe and highly effective combination for the treatment of ventricular tachycardia accompanying myocardial infarction in dogs. No fatalities have occurred during or soon after testing with Nupercaine in 21 animals. Using essentially similar methods, similar guides to effectiveness and dosage, and similar warnings of danger, fatalities did occur in the previously reported series of tests with quinidine lactate and gluconate,[14] procaine amide (Pronestyl),[15]

magnesium sulfate and chloride[16] and diphenylhydantoin sodium and phenobarbital.[17] These observations may be regarded as evidence that

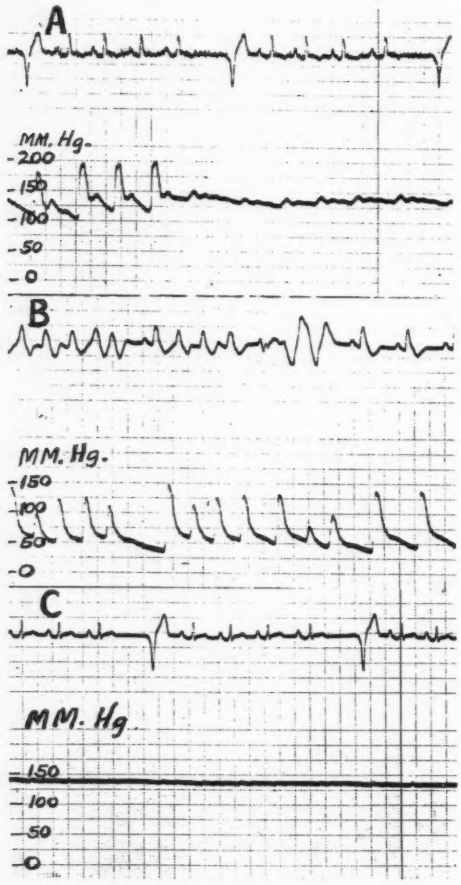

FIG. 6. Electrocardiograms showing durations of complexes, and blood pressures in experiment with development of intraventricular block due to rapid administration of Nupercaine. (*A*) After rapid infusion of Nupercaine, 6.5 mg. per kilogram. (*B*) Wide irregular QRS complexes after 7 mg. per kilogram. Note moderately well sustained blood pressure and large pulse pressures, even in the presence of wide electrocardiogram complexes. (*C*) Thirty seconds after stopping infusion. Recovery of normal electrocardiogram durations, and of mean blood pressure.

in effective dosage and with adequate electrocardiographic observation, treatment with phenobarbital and Nupercaine is safer than is effective treatment with any of the other drugs mentioned. In addition, the phenobarbital-Nupercaine treatment ranks high in terms of freedom from toxic side reactions. These results should lead to early clinical trials under carefully controlled conditions.

It should be emphasized that safety in the treatment of a severe ventricular tachycardia by any potent intravenously administered drug requires continuous observation with frequent records on a direct-writing electrocardiograph. These records then serve as guides to the adequacy of dosage and to degree of approach to detrimental overdosage as indicated by prolongation of P-R and QRS intervals, especially the latter.[14] Frequent blood pressure determinations should be a requirement also. Pronounced hypotensive effect should be regarded as a danger sign, even when the electrocardiogram fails to show impairment of conduction.[14]

The finding that phenobarbital or pentobarbital prevents toxic side reactions of Nupercaine in therapeutically effective doses might logically have been anticipated from reports of Tatum and co-workers[18-20] that barbital sodium alone or in combination with paraldehyde completely prevented cocaine convulsions in dogs and monkeys, and increased the lethal dose of cocaine by 300 to 400 per cent. Tatum and co-workers reported that morphine is ineffective as an antidote to cocaine. Other drugs found ineffective or deleterious in cocaine antidote tests were atropine, chloral hydrate and ether.

Although phenobarbital significantly increased the effectiveness and usefulness of Nupercaine and of dilantin sodium[17] as ectopic impulse suppressor compounds, generalizations concerning its possible usefulness in combination with other ectopic impulse suppressor substances are not justified in the absence of specific tests. Tests of quinidine compounds in combination with phenobarbital and pentobarbital are in progress. Barbiturates markedly increased the mortality in experiments with magnesium sulfate and chloride.[15] Knowledge of the nature of the processes by which ectopic impulses are produced, and of the mechanisms of action of suppressor drugs is far too insufficiently advanced to supply a

ational basis for predicting the efficacy of lrug combinations in this field.

Summary

Nupercaine hydrochloride administered intravenously by slow injection or constant venoclysis to dogs with ventricular tachycardia accompanying myocardial infarction exhibited ectopic impulse suppressor effects in each of 22 animals divided into four groups:

A. Nupercaine alone was effective in suppressing ectopic activity, but vomiting and convulsive movements commonly occurred and interfered with administration in some animals.

B. Morphine before Nupercaine prevented Nupercaine vomiting but did not prevent convulsive movements. Morphine did not enhance nor prolong ectopic impulse suppressor action.

C. Phenobarbital sodium before Nupercaine eliminated vomiting. Mild stretching of doubtful cause occurred in two of nine dogs during tests. Ectopic impulse suppressor effect was enhanced and markedly prolonged by the phenobarbital.

D. Pentobarbital sodium before Nupercaine eliminated vomiting and convulsive activity, and enhanced the ectopic suppressor effect, but did not prolong it.

Statistical evaluation of the reliability of the comparison of mean durations of ectopic suppressor action shows that the duration of control in the phenobarbital-Nupercaine experiments was significantly greater than in any other group.

No fatalities occurred in any group.

Blood pressure tended to rise or remain constant in all slow administration tests. P-R and QRS durations showed only minor alterations in such tests.

In some rapid administration tests, periods of prolonged QRS deflections and hypotension occurred. Upon stopping the fast infusion all signs returned to normal within 30 seconds.

The phenobarbital-Nupercaine combination is regarded as an effective and relatively safe combination for the treatment of ventricular tachycardia accompanying myocardial infarction when suitable precautions are observed.

Sumario Español

En 22 perros con taquicardia ventricular acompañada de infarto del miocardio, hidrocloruro de Nupercaína se encontró ser un supresor potente de impulsos ectópicos. Cuando la Nupercaína se usa sola también produce vómitos y movimientos convulsivos. Cuando se combinó con morfina, los vómitos se eliminaron pero las convulsiones no. Cuando se combinó con fenobarbital sódico o pentobarbital sódico, la acción de suprimir impulsos ectópicos fué aumentada y los vómitos y convulsiones suprimidos. La duracion de la acción de suprimir los impulsos ectópicos fué significativamente mayor en el experimento con fenobarbital y Nupercaína que en ningún otro grupo. Ninguna muerte ocurrió en los 22 perros.

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The Interrelationships of Serum Lipids in Men and Women Past Sixty-Five Years of Age and Their Bearing on Atherosclerosis

By MENARD M. GERTLER, M.D., AND BERNARD S. OPPENHEIMER, M.D.

The interrelationships of serum lipids, that is, free cholesterol, esterified cholesterol, total cholesterol, lipid phosphorus, total lipids, neutral fats and S_f 10–20 molecules were determined in 91 women and 38 men past the age of 65 years. It was observed that all the serum lipids with the exception of neutral fats were statistically higher in the women. Furthermore, it was shown that the serum total cholesterol and serum S_f 10–20 molecules were correlated to a significant degree in the men, $0.59 \pm .15$, but to an insignificant degree in the women, $0.21 \pm .12$. It was also shown that the levels of serum total cholesterol and S_f 10–20 molecules increase with age within the age range 65 to 85 in the women but remain stationary or actually decrease in the men. The bearing of these findings on atherosclerogenesis is discussed.

DURING the past three years, unprecedented progress has been accomplished in the study of atherosclerosis. Gofman and his co-workers[1-3] have called attention to a newer method of investigation which has stimulated many individuals to search for the unknown substance or substances causally related to atherosclerosis.

There are no known substances which have been proven to be causally related to human atherosclerosis, although there are many factors which are associated with the development of atherosclerosis in humans. These entities which are found in the serum include cholesterol (free, esterified and total),[4-6] lipid phosphorus,[7,8] total lipids and neutral fats,[9] S_f 10–20 molecules[1-3] and alpha and beta lipoproteins.[10, 11] One or more of the substances, while not by themselves causally related to atherosclerosis, may actually be a gross reflection of the metabolic error.[7]

It has been well documented that one or more of these chemical entities occur in excessive amounts in the sera of humans who overtly manifest atherosclerosis. With the development of thought as to the genesis of atherosclerosis, it has been possible to replace the classic concept that the serum cholesterol is the best index to atherosclerosis and replace it with the tenet that the interrelationship of the blood lipids is by far a better guide to the genesis of atherosclerosis than is any single lipid variable.[7, 12]

An observation which requires further amplification is the lowering of serum total cholesterol after the sixth decade in males.[13, 14] It is not known (a) whether this is due to an actual lowering of the serum total cholesterol or (b) whether it is merely an indication that those individuals with the higher serum cholesterol values are absent at the older ages or (c) whether it merely indicates a value for a selective population of long-lived individuals.

It may be possible by the study of serum lipids in this older age group to obtain a clue which would help to explain the preponderance of males in contrast to females who experience atherosclerosis.[15, 16]

Accordingly, the present communication will report on a study of serum lipids in 38 males and 91 females who have attained the age of 65 or more in good general health.

METHODS AND MATERIALS

This study was undertaken on 38 men whose age averaged 77 years (range, 65 years to 86 years) and 91 women whose age averaged 75 years (range, 65 years to 86 years). The men and women selected for this study lived in the institution for reasons other than those of health. Most of them entered the institution in part for economic reasons and in

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part to have a home in their old age. They were able to take care of themselves and did not have any history of a major illness, for example, diabetes, which is known to affect the serum lipids. The men and women described in this study were under similar conditions of diet, exercise, and living habits. The national origin of these individuals varied from England, Germany and other European countries to the United States of America. Thus, the men and women in this study were comparable from a racial and national origin, environment, dietary intake and socio-economic status. In addition, the element of nutritional status was considered in this survey and found not to have any bearing on the comparison of the lipids.

Fasting venous blood was drawn on these 38 men and 91 women, and permitted to clot at room temperature; serum separation was completed within four hours after the blood was drawn. Serum cholesterol (free, esterified and total) was determined by the Schoenheimer-Sperry technic.[17, 18] Lipid phosphorus was determined on an aliquot from the filtrate by the Fiske-Subbarow technic.[19] Total lipids were determined on a 1.0 ml. sample of serum, extracted with a Bloor reagent; the filtrate was evaporated to dryness, hydrochloric acid solution was added, and the residue was redissolved with petroleum ether; the determination was then made gravimetrically.[20]

Neutral fats were calculated by means of the following formula:

Neutral fats = Total lipids minus [(1.5 × total cholesterol) plus (2.5 × lipid phosphorus)].

The technic for total lipids is not entirely without error, but it is useful as a measure of difference between the two groups inasmuch as the error is probable a constant and systematic one.

Dr. John Gofman was kind enough to arrange for the partition into S_f molecules of an aliquot of serum which was forwarded to him by air express in ice-cooled containers.

In this report, 14 individuals (two men and 12 women) had only one sample of blood for analysis, 79 individuals (20 men and 59 women) had two samples of blood for analysis, nine individuals (five men and four women) had three samples of blood for analysis, 12 individuals (five men and seven women) had four samples of blood for analysis and 15 individuals (six men and nine women) had five samples of blood for analysis. Accordingly, as far as cholesterol (free, esterified and total) and lipid phosphorus are concerned, in the 38 values reported for the 38 men, there were 107 samples of blood drawn; and in the 91 values reported for the 91 women, there were 205 samples of blood drawn. The analysis of neutral fats, total lipids and S_f 10–20 molecules was not attempted until this project had been started and thus fewer determinations are available. However, there were 48 determinations made of total lipids and neutral fats in the 23 men whose values are reported. Similarly, there were 95 determinations made on the 65 women whose values are reported for total lipids and neutral fats. The S_f 10–20 molecules partition is available on all the men and represents 62 total analyses. There are only 69 S_f 10–20 molecules partition on the 91 women. This represents 90 total analyses.

Results

The results of the biochemical determinations are to be considered under the following separate sections: (1) serum free cholesterol, (2) serum esterified cholesterol, (3) serum total cholesterol, (4) serum total lipids, (5) serum lipid phosphorus, (6) S_f 10–20 molecules (Gofman), and (7) serum neutral fats.

In addition to these lipid values, various ratios were also determined; namely: (1) free cholesterol-esterified cholesterol, (2) esterified cholesterol-total cholesterol, and (3) total cholesterol-lipid phosphorus.

1. Serum Free Cholesterol

The serum free cholesterol was higher in the 91 women in contrast to the level of serum free cholesterol in the 38 men, that is, 74.15 ± 1.43 mg. per 100 cc. and 60.15 ± 2.22 mg. per 100 cc., respectively (table 1). These results are also statistically significant: $p < .001$. This amount of free cholesterol is equal to 26.8 per cent of the total cholesterol in both the men and women, an amount almost identical with 26.9 per cent reported by Sperry.[21] Similar reports have been made by Konerup.[22]

2. Serum Esterified Cholesterol

The level of serum esterified cholesterol was higher in the 91 women as compared with the 38 men, that is, 208.08 ± 3.94 mg. per 100 cc. and 167.66 ± 11.7 mg. per 100 cc., respectively (table 2). These differences are also statistically significant, $p < .001$. These values are in keeping with other published data[13, 23] and differ from still others.[22, 24] The differences are probably due to the age difference and the technics involved.

3. Serum Total Cholesterol

Again, it was observed that the average level of serum total cholesterol is higher in the

91 women in comparison with the 38 men (table 3). It is noteworthy that if serum total cholesterol were the limiting factor in the genesis of atherosclerosis, then it would be expected that the women would show a greater degree of atherosclerosis than the men. However, as will be shown subsequently, the total cholesterol-lipid phosphorus ratio is statistically equal in both groups. This may help to explain the comparative freedom from atherosclerosis in both groups despite the increased level of serum total cholesterol in the women. The values of serum total cholesterol for the men reported in this presentation are in keeping with other published data.[13, 22, 23] The values reported for serum total cholesterol in the women, however, are much higher than in other reports.[22, 24, 25, 26]

TABLE 1.—*Comparison of the Levels of Serum Free Cholesterol in 91 Women and 38 Men Above the Age of 65 Years**

Milligrams per cent	Women Number	Men Number
30- 34.9	0	1
35- 39.9	1	0
40- 44.9	0	4
45- 49.9	1	5
50- 54.9	2	6
55- 59.9	9	3
60- 64.9	13	3
65- 69.9	10	9
70- 74.9	17	2
75- 79.9	10	2
80- 84.9	5	0
85- 89.9	11	2
90- 94.9	6	1
95- 99.9	3	0
100-104.9	2	0
105-109.9	0	0
110-114.9	1	0
Total	91	38
Mean ± standard error	74.15 ± 1.43	60.15 ± 2.22
Standard deviation	13.65	13.65
Critical ratio	5.3 ($p < .001$)	

* At the request of the Editor, tables showing the actual values of the various serum lipids in each of the 129 subjects are being omitted. These data will be furnished on request.

4. Serum Total Lipids

The serum total lipids contain not only the phosphorus-containing lipids which are predominantly represented by lecithin and cephalin but also the nonphosphorus-containing lipids. As in the case of the other lipids, the 65 women again possessed more total lipids on the average than the 23 men, that is, 981.1 ± 17.4 mg. per 100 cc. and 755.4 ± 31.0 mg. per 100 cc. (table 4). Significance of this difference is $p < .001$. These values are almost identical with values observed by Konerup in women of similar ages, but lower than the values reported by the same author in men of similar ages. There are several reports of total lipid values in men and women of the third and fourth decades.[22, 27] These values are much

TABLE 2.—*Comparison of the Levels of Serum Esterified Cholesterol in 91 Women and 38 Men Above the Age of 65 Years*

Milligrams per cent	Women Number	Men Number
80- 89	0	0
90- 99	1	0
100-109	0	2
110-119	1	1
120-129	0	3
130-139	1	5
140-149	2	3
150-159	1	3
160-169	4	5
170-179	12	3
180-189	8	3
190-199	13	2
200-209	6	2
210-219	10	3
220-229	10	1
230-239	6	1
240-249	1	1
250-259	5	0
260-269	3	0
270-279	3	0
280-289	1	0
290-299	1	0
300-309	2	0
Total	91	38
Mean ± standard error	208.08 ± 3.94	166.1 ± 5.8
Standard deviation	37.60	36.0
Critical ratio	6.00 ($p < .001$)	

lower than those values reported by others in age groups similar to those in this paper. This raises the question as to whether there is a rise in total lipids with age. The answer is probably in the affirmative.

5. Serum Lipid Phosphorus

It is observed, as in the case of the serum cholesterol (free, esterified and total), that there is a statistically significant ($p < .001$) greater amount of lipid phosphorus in the serum from the 91 women than in the serum from the 38 men, that is, 12.16 ± .34 mg. per 100 cc. and 10.27 ± 0.27 mg. per 100 cc. respectively (table 5). It should be pointed out again that in spite of the greater amounts of total cholesterol and lipid phosphorus in the serum taken from the women, the ratio total cholesterol-lipid phosphorus remains unchanged. (See next section.) These values are somewhat higher than others reported in the literature for similar age groups,[22, 25] but there is general unanimity that serum lipid phosphorus is higher in women than in men.[22, 26] Again the difference in age may account for the lower values reported by the other authors.

TABLE 3.—*Comparison of the Levels of Serum Total (Free and Esterified) Cholesterol in 91 Women and 38 Men above the Age of 65 Years*

Milligrams per cent	Women Number	Men Number
130–149	0	1
150–169	2	3
170–189	1	6
190–209	2	4
210–229	6	9
230–249	15	3
250–269	15	4
270–289	13	5
290–309	14	1
310–329	6	2
330–349	5	0
350–369	9	0
370–389	0	0
390–409	3	0
Total	91	38
Mean ± standard error	282.7 ± 5.10	226.3 ± 7.77
Standard deviation	51.0	47.8
Critical ratio of the means	6.0 ($p < .001$)	

6. S_f 10–20 Molecules

The sole reports on S_f 10–20 molecules stem from Gofman's laboratory.[1-3] Gofman and co-workers have reported the S_f 10–20 molecules in 16 women from 61 to 70 years of age and in 37 men from 61 to 70 years of age. The data which are presented here represent not only a larger series, but also an older age group. The trend reported herein is entirely in keeping with Gofman's observations and extends them. The women, doubtless, possess a statistically significant higher amount of S_f 10–20 molecules in the serum than the men. (See table 6 and fig. 1.)

TABLE 4.—*Comparison of the Levels of Serum Total Lipids in 65 Women and 23 Men above the Age of 65 Years*

Milligrams per cent	Women Number	Men Number
450– 499	0	1
500– 549	0	2
550– 599	0	1
600– 649	0	3
650– 699	2	0
700– 749	2	2
750– 799	3	5
800– 849	5	2
850– 899	8	2
900– 949	6	1
950– 999	13	2
1000–1049	9	1
1050–1099	5	0
1100–1149	2	1
1150–1199	5	0
1200–1249	1	0
1250–1299	1	0
1300–1349	3	0
Total	65	23
Mean ± standard error	981.2 ± 17.4	755.5 ± 31.01
Standard deviation	150.1	104.5
Critical ratio	7.0 ($p < .001$)	

7. Serum Neutral Fats

In this single instance the level of the serum lipid considered was not significantly increased

in the women. The full interpretation of this will be left for the discussion. The serum neutral fats are lower than other values reported in the literature.[28] The values given here are higher than those reported in eight young women, ages 20 to 38, by Boyd.[27] Part of these differences may be explained (a) by the mutability of the neutral fats, (b) by the lower total cholesterol and lipid phosphorus values and (c) by age differences.

TABLE 5.—*Comparison of the Levels of Serum Lipid Phosphorus in 91 Women and 38 Men above the Age of 65 Years*

Milligrams per cent	Women Number	Men Number
7.0- 7.49	0	2
7.5- 7.99	0	3
8.0- 8.49	2	1
8.5- 8.99	0	4
9.0- 9.49	0	3
9.5- 9.99	3	7
10.0-10.49	7	4
10.5-10.99	9	3
11.0-11.49	10	2
11.5-11.99	10	4
12.0-12.49	7	2
12.5-12.99	13	0
13.0-13.49	9	0
13.5-13.99	5	3
14.0-14.49	8	0
14.5-14.99	4	0
15.0-15.49	2	0
15.5-15.99	2	0
Total	91	38
Mean ± standard error	12.16 ± 0.34	10.27 ± 0.27
Standard deviation	3.21	1.63
Critical ratio	4.5 ($p < .001$)	

8. Free Cholesterol-Esterified Cholesterol

The ratio of free cholesterol to esterified cholesterol in the serum is similar to the ratio reported by others employing similar methods for biochemical determinations.[13, 21] These values are recorded in table 8.

The average of the ratio serum free cholesterol-serum esterified cholesterol is the same in the two groups.

9. Esterified Cholesterol-Total Cholesterol

The ratio of esterified cholesterol to total cholesterol in the serum did not differ significantly in the two groups. These results are similar to those published by other investigators employing similar methods.[10, 13, 21]

TABLE 6.—*Comparison of S_f 10-20 Molecules in 69 Women and 38 Men above the Age of 65 Years*

Milligrams per cent	Women Number	Men Number
20- 29	1	3
30- 39	4	6
40- 49	12	7
50- 59	19	6
60- 69	5	6
70- 79	8	4
80- 89	7	4
90- 99	2	0
100-109	2	1
110-119	4	1
120-129	2	0
130-139	0	0
140-149	1	0
150-159	1	0
160-169	0	0
170-179	1	0
Total	69	38
Mean ± standard error	70.3 ± 3.6	57.4 ± 3.5
Standard deviation	30.1	21.4
Critical ratio	2.56 ($p < .001$)	

10. Total Cholesterol-Lipid Phosphorus

The ratio of total cholesterol to lipid phosphorus is the same in the two groups. This is noteworthy for both the serum total cholesterol and the serum lipid phosphorus are statistically higher in the women than the men, but when the two results are formed into a ratio, there is no statistically significant difference. This observation lends support to the concept that the ratio of total cholesterol to lipid phosphorus is by far of greater importance than either serum total cholesterol or serum lipid phosphorus in assessing the genesis of atherosclerosis.[4, 7, 8]

From table 11, it may be seen that only two correlations are statistically significant: (a)

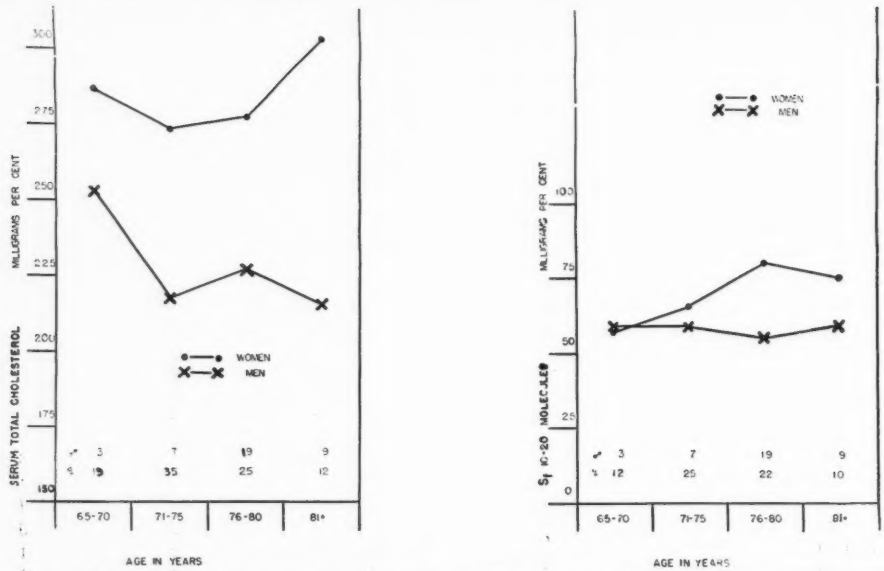

FIG. 1. The values are shown of serum total cholesterol and S_f 10–20 molecules in the men and the women at various age groups past the age of 65. Note the rise and decline in the levels of serum total cholesterol in the women and men respectively. The S_f 10–20 molecules show no fluctuation in the men and a steady rise in the women.

TABLE 7.—*Comparison of the Serum Neutral Fats in 65 Women and 23 Men above the Age of 65 Years*

Milligrams per cent	Women Number	Men Number
00–49	0	1
50–99	1	4
100–149	10	4
150–199	14	7
200–249	14	2
250–299	10	1
300–349	5	2
350–399	3	1
400–449	3	1
450–499	4	0
500–549	0	0
550–599	0	0
600–649	1	0
Total	65	23
Mean ± standard error	227.4 ± 7.5	183.7 ± 21.9
Standard deviation	93.0	100.5
Critical ratio	1.9 ($p < 0.5$)	

TABLE 8.—*Comparison of the Ratio of Serum Free Cholesterol to Serum Esterified Cholesterol in 91 Women and 38 Men above the Age of 65 Years*

Ratio in Percentage	Women Number	Men Number
28.0–30.9	5	5
31.0–33.9	18	8
34.0–36.9	45	11
37.0–39.9	14	6
40.0–42.9	3	3
43.0–45.9	1	1
46.0–48.9	1	4
49.0–51.9	0	0
52.0–54.9	1	0
55.0–57.9	1	0
58.0–60.9	0	0
61.0–63.9	2	0
Total	91	38
Mean ± standard error	36.49 ± .40	36.52 ± .84
Standard deviation	3.8	5.2
Critical ratio	(No difference)	

in the men between S_f 10–20 molecules and total cholesterol and, (b) in the women between age and S_f 10–20 molecules. These correlations are noteworthy and suggest that since S_f 10–20 molecules are highly correlated

TABLE 9.—*Comparison of the Ratio of Serum Esterified Cholesterol to Serum Total Cholesterol in 91 Women and 38 Men above the Age of 65 Years*

Ratio in Percentage	Women Number	Men Number
56.0–57.9	2	0
58.0–59.9	0	0
60.0–61.9	0	0
62.0–63.9	0	1
64.0–65.9	1	0
66.0–67.9	2	0
68.0–69.9	1	3
70.0–71.9	2	3
72.0–73.9	19	7
74.0–75.9	45	12
76.0–77.9	17	11
78.0–79.9	2	1
Total	91	38
Mean ± standard error	74.2 ± .34	74.2 ± 0.50
Standard deviation	3.44	3.08
Critical ratio	(No difference)	

TABLE 10.—*Comparison of the Ratio of Serum Total Cholesterol to Lipid Phosphorus in 91 Women and 38 Men above the Age of 65 Years*

Ratio in Percentage	Women Number	Men Number
16.0–16.9	0	1
17.0–17.9	2	0
18.0–18.9	1	3
19.0–19.9	6	2
20.0–20.9	7	4
21.0–21.9	13	4
22.0–22.9	14	8
23.0–23.9	15	5
24.0–24.9	15	4
25.0–25.9	9	3
26.0–26.9	4	1
27.0–27.9	1	1
28.0–28.9	2	2
29.0–29.9	1	0
30.0–30.9	0	0
31.0–31.9	1	0
Total	91	38
Mean ± standard error	23.2 ± .27	22.3 ± .44
Standard deviation	2.72	
Critical ratio	(No difference)	

ith atherosclerosis, the level of serum total holesterol may be employed as a guide to the

TABLE 11.—*Correlations between Age, Serum Total Cholesterol and S_f 10–20 Molecules*

Correlation	Women	Men
Age and total cholesterol	+0.05 ± .14	−0.13 ± .19
S_f 10–20 molecules and total cholesterol	+0.21 ± .12	+0.59 ± .15*
Age and S_f 10–20 molecules	+0.31 ± .10*	−0.05 ± .16

* Significant.

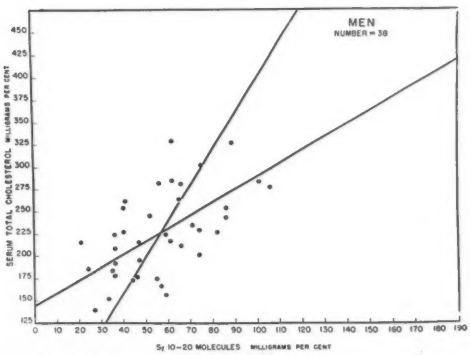

FIG. 2. Scattergram with regression lines showing a significant positive correlation of + .59 ± .15 between serum total cholesterol and S_f 10–20 molecules in the 38 men past the age of 65.

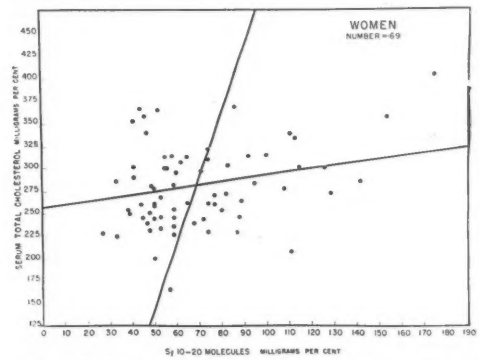

FIG. 3. Scattergram with regression lines showing an insignificant positive correlation of + .21 ± .12 between serum total cholesterol and S_f 10–20 molecules in the 91 women past the age of 65.

degree of atherosclerosis in men with much better success than in women. (See figs. 2 and 3.) These correlations are also in keeping with Gofman's observations that the S_f 10–20

molecules do not change in men after the mid-thirties, but do continue to rise steadily in women. Perhaps the female has additional protective mechanisms which, in spite of the high concentration of S_f 10–20 molecules in the serum, exert a salutary effect. This will be considered in the discussion.

By applying the technic of partial correlation to the relationship of age, serum total cholesterol and S_f 10–20 molecules, it was found that in the men, the correlation between serum total cholesterol and S_f 10–20 molecules with the factor of age removed is +0.58. This correlation was insignificant in the women, i. e., +0.20. The correlation in women between age and S_f 10–20 molecules with the effect of serum total cholesterol nullified is +0.31 and in men, −.06. These data may be interpreted as meaning that in men, in contrast to women, the relationship between the S_f 10–20 molecules and serum total cholesterol is constant in spite of age. In addition, in contrast to men, there is a steady rise in S_f 10–20 molecules in the women which has no bearing on the level of serum total cholesterol. (See fig. 4.)

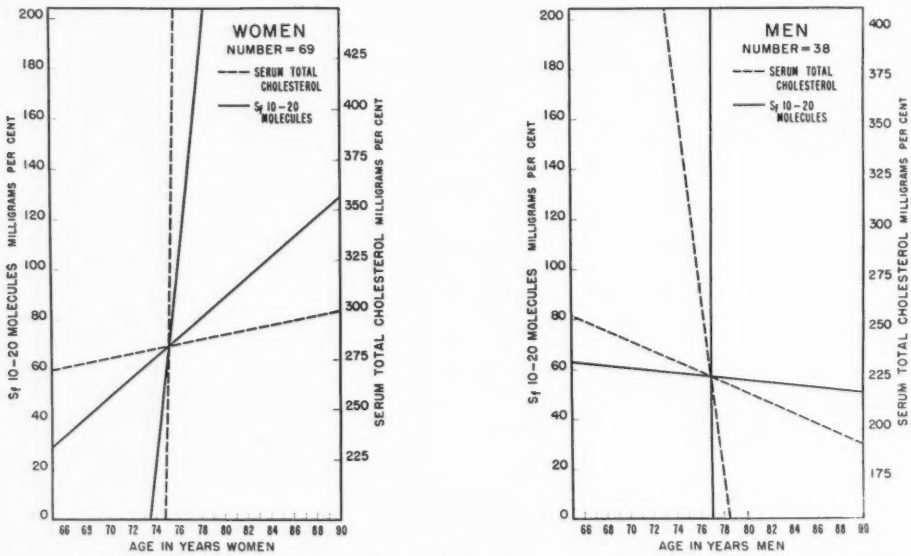

FIG. 4. Diagram on the left reveals the significant positive correlation ($r = +.31 \pm .10$) and insignificant correlation ($r = +.05 \pm .14$) between age and S_f 10–20 molecules and serum total cholesterol respectively in the 91 women past the age of 65.

Diagram on the right reveals the insignificant correlations in the 38 men past 65 years of age between age and serum S_f 10–20 molecules ($r = -.13 \pm .19$) and between age and serum total cholesterol ($r = -.05 \pm .16$).

DISCUSSION

This study of the interrelationship of serum lipids in 38 healthy men over 65 years of age and 91 healthy women over 65 years of age revealed several new facts, confirmed others and extended still others.

Although it has been demonstrated that there is a difference in the distribution of serum lipids between men and women, a satisfactory series of the older age groups is not available for the comparison of the total lipid pattern. It is noteworthy that the women as a group possessed higher levels of cholesterol (free, esterified and total) in the serum than did the men. The first basic question presents itself at this juncture. If the level of cholesterol (free, esterified and total) in the serum were the limiting factor or perhaps a threshold factor in the genesis of atherosclerosis then i

would be reasonable to expect the women to evidence a greater degree of atherosclerosis. From the examination of the health records and clinical findings, there is no evidence for this expectation.

On examining the values of other serum lipids, that is, lipid phosphorus, total lipids and neutral fats, it was found that the average serum values in the women exceeded the average serum values in the men by significant amounts in all instances except the neutral fats. In searching for a suitable explanation for this difference, no obvious answer is immediately apparent. There are, however, several tenable explanations. It has been demonstrated in men that there is a correlation of $+0.26 \pm .08$ between serum total cholesterol and obesity while there is a correlation of $-0.18 \pm .08$ between serum total cholesterol and linearity.[29] Similarly, the correlation in men between serum lipid phosphorus and obesity is $-0.23 \pm .08$ and between lipid phosphorus and linearity is $-0.21 \pm .08$. Since women possess more fatty tissue than men per unit of weight,[30] it is not surprising to find the higher values of serum total cholesterol and lipid phosphorus in the women. In addition, there appears to be almost complete unanimity that female sex hormones or physiologically similarly acting hormones increase the serum lipids appreciably. These include estradiol benzoate[31, 33] and diethylstilbestrol.[32-37] Women past the age of 65 have a low estrogen titer.[38] Whether the serum lipid pattern establishes itself in women at the peak of the estrogen output and then remains at that level is unknown.

In a study made on males subjected to bilateral orchidectomy and given 500 mg. diethylstilbesterol daily, a rise in all lipids was observed, particularly the lipid phosphorus and total lipids.[39]

Thus, there appears to be no doubt that female sex hormones do increase the serum phosphorus, serum total lipids, neutral fats and serum total cholesterol. The available data on male sex hormones are not as plentiful, but several reports do show that they exert virtually no effect on the serum lipid level.[40-43]

Gofman and associates[3] have presented convincing evidence that there is a high degree of correlation ($r = 0.8$) between the S_f 10–20 molecules and the degree of atherosclerosis. These facts have been founded on much data with extremely judicious analysis of the data. In the present series of men and women past the age of 65, it has been found that the women have a higher value of S_f 10–20 molecules than the men (70 mg. per 100 cc. to 57 mg. per 100 cc.). It would be reasonable, therefore, to assume from the evidence presented by Gofman that the women should be more atherosclerotic than the men. Based on such signs as fundus examination, x-ray appearance of the aorta, blood pressure and electrocardiographic evidence, there is virtually no difference between the men and the women. It has long been known that women do not experience atherosclerosis to the same degree as men in the younger years and that the development of atherosclerosis in women requires many more years than in men (based on statistics of death rate in the older age groups).[44] Accordingly, it is reasonable to suggest that there exists in women an unknown intrinsic factor which prevents the development of atherosclerosis in spite of higher serum total cholesterol levels and/or S_f 10–20 molecules.

Additional evidence to support this hypothesis stems from figure 14 of Gofman's paper,[3] which clearly shows similar levels of S_f 10–20 molecules in the sixth decade in both men and women; yet, it has been established by various groups that the peak of the male incidence of atherosclerosis, as judged solely by coronary heart disease, is at that age, with four males to one female dying from this cause.

Gofman states: "The female at 50 to 60 years of age is essentially equivalent to the male of that age in S_f 10–20 level, or in atherosclerogenesis, so that each year that passes. reduces the relative protection of her relatively lower atherosclerogenicity of earlier years." Gofman states also that there is a steady rise in S_f 10–20 molecules in females. This, again, is in keeping with the results reported here.

It is well known that women, prior to the menopause, who have clinical atherosclerosis, as manifested by coronary heart disease,

usually have had long standing hypertensive cardiovascular disease,[45] diabetes mellitus[46] or xanthomatosis.[47] Furthermore, it is known that the incidence of atherosclerosis in the female increases following the menopause. Women show a steady rise in S_f 10–20 molecules from the age of 25, but do not show any rise in incidence of atherosclerosis at the time of the menopause. Accordingly, it is reasonable to assume that in women, the only limiting factor in atherosclerosis is not necessarily the S_f 10–20 molecules, but additional factors may play a role. These possibly include intimal permeability, thickness of the coronary arteries, or loss of estrogens which may actually be reflected by the aforementioned factors or even regulate them.

Summary and Conclusions

1. A study has been made of the interrelationships of serum lipids in 38 men and 91 women who have lived past the age of 65 without any recorded illness known to affect or be associated with abnormal lipid metabolism. The individuals were comparable racially, socio-economically and nutritionally.

2. It was observed that the women possessed statistically higher levels of all serum lipids except neutral fats than the men:—free cholesterol: 74.2 ± 1.43 and 60.2 ± 2.22, respectively; esterified cholesterol: 208.1 ± 3.94 and 167.7 ± 11.70, respectively; total cholesterol: 282.7 ± 5.10 and 226.3 ± 7.77, respectively; total lipids: 981.2 ± 17.40 and 755.3 ± 31.01, respectively; lipid phosphorus: 12.2 ± 0.34 and 10.3 ± 0.27, respectively; S_f 10–20 molecules: 70.3 ± 3.60 and 57.4 ± 3.50, respectively; neutral fats: 227.4 ± 7.50 and 183.7 ± 21.90, respectively.

3. The ratios free cholesterol-esterified cholesterol, esterified cholesterol-total cholesterol, and total cholesterol-lipid phosphorus did not show any significant differences between the men and women: 36.5 ± 0.40 and 36.5 ± .84; 74.2 ± 0.34 and 74.2 ± 0.50; 23.2 ± 0.27 and 22.3 ± 0.44, respectively.

4. From the evidence presented, it is reasonable to suggest that S_f 10–20 (Gofman) molecules may not have the same significance in the genesis of atherosclerosis, as evidenced by coronary heart disease, in women as in men.

5. The relationship between serum total cholesterol and S_f 10–20 molecules is significant in the men ($r = 0.59 \pm .15$) and not significant in the women ($r = 0.21 \pm .12$).

6. In the women, in contrast to the men, there is a steady rise in the S_f 10–20 molecules past the age of 65. ($r = .31 \pm .10$). The serum total cholesterol has an insignificant upward trend in the women and an insignificant downward trend in the men.

Acknowledgments

The authors are indebted to Dr. Frederic D. Zeman, Chief of Medical Services of the Home for the Aged and Infirm Hebrews for his wholehearted cooperation and assistance during this study. To Dr. John W. Gofman, the authors are very grateful for his analysis of the serum into S_f 10–20 molecules and his advice on this problem. Thanks are due to Miss Frances Aezen for technical assistance. Also to the nurses, internes and other members of the staff of the Home for the Aged and Infirm Hebrews, we should like to express our appreciation for their cooperation.

Sumario Español

Las interrelaciones de los lípidos del suero, i.e., colesterol libre, colesterol esterificado, colesterol total, fósforo lípido, lípidos totales, grasas neutrales y moléculas S_f 10–20 fueron determinadas en noventa y una mujer y treinta y ocho hombres sobre la edad de 65 años. Se observó que todos los lípidos del suero con la excepción de grasas neutrales fueron estadísticamente más altos en la mujer. Además, se demostró que el colesterol total del suero y las moléculas S_f 10–20 del suero estaban correlacionadas en un grado significativo en los hombres, viz., 0.59 ± 0.15, pero en un grado poco significativo en la mujer, viz., 0.21 ± 0.12. También se demostró que los niveles del colesterol total del suero y de las moléculas S_f 10–20 aumentan con la edad entre los 65–85 años en la mujer pero permanecen estacionarios o actualmente disminuyen en los hombres. El significado de estos hallazgos en la ateroesclerogenesis se discute.

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A Study of the Relationship between Unipolar Leads and Spatial Vectorcardiograms, Using the Panoramic Vectorcardiograph

By WILLIAM R. MILNOR, M.D., SAMUEL A. TALBOT, PH.D., AND ELLIOT V. NEWMAN, M.D.

The extent to which precordial and other unipolar leads are influenced by the proximity of the exploring electrode to one part or another of the heart is the subject of considerable debate. One approach to the problem is to determine how closely precordial leads can be predicted from spatial vectorcardiograms recorded by leads relatively remote from the heart. The panoramic vectorcardiograph described below provides a convenient way of doing this, since it automatically records scalar derivations from the vectorcardiogram for any spatial axis. Results indicate that local effects are not the predominant factor in determining the form of the complexes in precordial leads.

ALTHOUGH "unipolar" chest and extremity leads are now widely used in clinical electrocardiography, there is still considerable diversity of opinion about just what part of the electrical activity of the heart is recorded by such leads. Two more or less conflicting theories have been proposed: (1) that unipolar leads are "semidirect" leads, influenced principally by the electrical state of the myocardium underlying the exploring electrode, (2) that they represent summations of the electrical activity in all parts of the heart.

The first theory was introduced by Wilson and his co-workers,[11, 12] on the basis of experiments in dogs which showed that the complexes recorded by unipolar leads from the chest wall closely resembled those recorded by direct unipolar leads from the underlying epicardial surface. They concluded that unipolar leads provided a way of isolating to some extent the electrical activity of different parts of the heart. This theory has been widely accepted in the current literature, and has been used in clinical electrocardiography as the basis for the concept of "electrical position of the heart,"[12] and in the electrocardiographic determination of anatomic position and rotation of the heart.[4]

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The second theory is essentially that employed by Einthoven in his calculation of mean electrical axes from the standard extremity leads.[3] Einthoven's hypothesis included only the frontal plane, but Duchosal and Sulzer,[1] as a result of their work in spatial vectorcardiography, concluded that this hypothesis was valid for any plane, and for any lead on the body surface. According to this view, the complex spread of electrical activity through the heart can be represented at any instant as a single equivalent dipole, and the voltage recorded by a precordial or other lead will be determined by the relation between the axis of the lead and the axis of the dipole, as well as the distance between the lead electrodes and the dipole. Since the spatial vectorcardiogram is a record of the variations in potential and direction of this single equivalent dipole, the form of the complexes in a precordial lead depends on the angle from which the lead "views," so to speak, the spatial vectorcardiogram. If this hypothesis is true, then it should be possible to predict the precordial electrocardiogram from a properly recorded spatial vectorcardiogram. Duchosal found it possible to do this in most cases, although there were occasional marked discrepancies.[2]

Although any complex electrical generator resembles a single dipole source when viewed from a sufficiently great distance, it has been generally supposed that precordial leads were too close to the heart for the Einthoven hypothesis to apply. Duchosal's results suggested

that this may not be true, and that further investigation was indicated.

The comparison of the electrocardiograms actually recorded from the precordium with the complexes predicted from the spatial vectorcardiogram is a good method of testing these hypotheses, for if the precordial leads are dominated by local effects, these local characteristics should not be apparent in the relatively remote leads from which the vectorcardiogram is recorded. The complexes predicted for the precordial area from the spatial vectorcardiogram would then differ from those actually recorded by precordial leads. In practice, however, this approach presents several difficulties. First, in order to predict from the vectorcardiogram the variations in potential at a given point it is necessary to define the spatial position of that point with respect to the nullpoint of the vectorcardiogram, that is, with respect to the electrical nullpoint in the body. Although the postulated existence of an electrical zero point in the body is a useful theoretic concept, the criteria for establishing its anatomic position are open to question, and most investigators have resorted to some arbitrary location such as the center of the ventricular mass determined radiologically.[1]

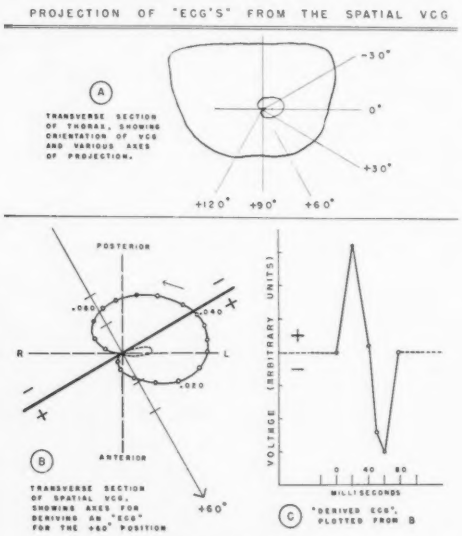

FIG. 1. Method of predicting the scalar electrocardiograms at points on the body surface from the vectorcardiogram. In *A* an arbitrary locus for the nullpoint has been selected, and the orientation of the transverse vectorcardiogram with respect to the thoracic wall is shown. *B* shows in more detail the relation of the loops to the +60 degree axis. The QRS loop is shown as a solid line with open circles indicating time intervals of 4.0 milliseconds, and is inscribed in a counter-clockwise direction. The T loop is shown as a broken line, and the P loop has been omitted. The heavy line through the nullpoint at right angles to the + 60 degree axis divides the electrical field into areas of positivity and negativity for this particular axis. The parts of the vectorcardiogram which lie in the positive half of the field will be recorded by a scalar unipolar lead along this axis as positive deflections, and those parts in the negative half of the field as negative deflections. The scalar QRS complex which would be expected at the point where the +60 degree axis intersects the chest wall can therefore be plotted as shown in *C*.

Second, since the spatial vectorcardiogram is usually recorded in terms of its projection on three planes (frontal, sagittal, and transverse), it is possible to calculate the predicted electrocardiograms only for points which lie in these planes. For all other points either measurements on a three-dimensional model of the spatial vectorcardiogram, or lengthy mathematic calculations, are needed.

Third, the accurate calculation of predicted potential variations from even a plane vectorcardiogram is an exacting and time-consuming operation. The method is discussed in detail by Duchosal,[1] and an example is given in figure 1, which shows the relationship between a transverse plane vectorcardiogram and the scalar* electrocardiogram to be expected in a specified direction in the electrical field.

To overcome some of these difficulties, we have adopted a method described by Schmitt in 1947 for the cathode-ray presentation of three-dimensional data.[8] His paper presents the mathematic transformations needed to convert three-dimensional data into any desired plane projection, and shows that this can be accomplished electrically by the use of sine-cosine potentiometers. These are simply rotat-

* The term "scalar" is used to distinguish conventional electrocardiograms, which measure the magnitude of the potential difference between two electrodes, from vectorcardiograms, which deal with spatial direction as well as magnitude.

ing variable resistors, which attenuate the voltages reaching them proportionately to the sine or cosine of the angle through which they are rotated.

Using the principles he outlined, we have designed an instrument, shown in figure 2, which makes it possible to display on a cathode ray oscilloscope any "view" of the spatial vectorcardiogram, or the scalar derivations from the vectorcardiogram along any axis drawn from the nullpoint in any direction in space. Because this machine enables one to "view" the spatial vectorcardiogram from any angle, we have called it the "panoramic" vectorcardiograph.

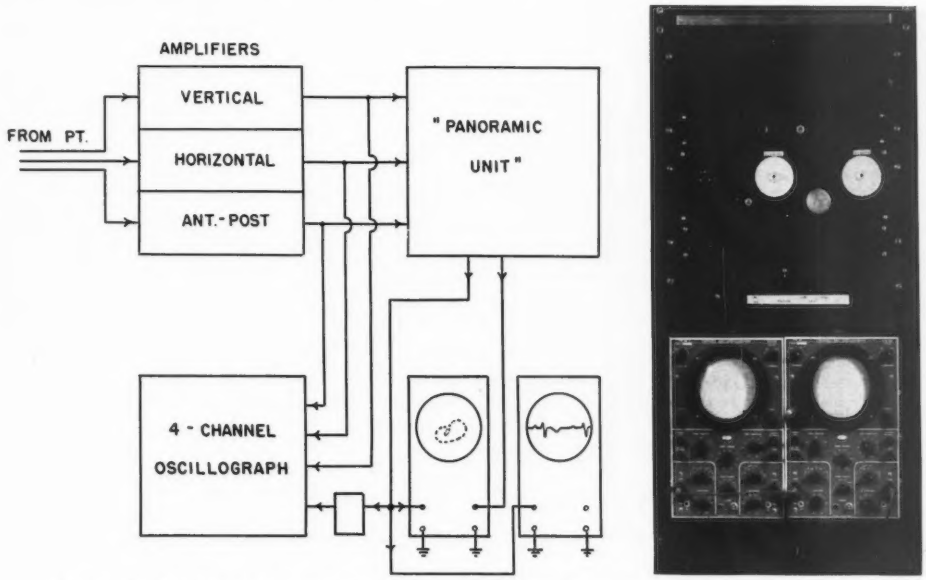

FIG. 2. Block diagram of panoramic vectorcardiograph. The panoramic unit and its cathode ray oscilloscopes are shown in the photograph on the right.

TECHNIC

Figure 2 shows a block diagram of the panoramic vectorcardiograph, with a photograph of the panoramic unit and its oscilloscopes. The vectorcardiograph (VCG) lead system used in this study is an orthogonal, bipolar system with a common electrode on the back of the right shoulder. The horizontal and anterior-posterior leads lie in the transverse plane passing through the junction of the second rib and the sternum. The electrodes of the horizontal lead are placed at this level, just medial to the posterior axillary line on the right and left back. The electrode so placed on the patient's right side is common to all three leads, and is paired with an electrode directly anterior to it, on the ventral surface of the right shoulder, for the anterior-posterior lead. The common electrode is paired with one vertically below it on the right lower back to make up the vertical lead. The lower right back electrode is placed so that the length of the vertical lead is the same as that of the horizontal lead. Standardization is the same in all three leads, no correction factor being used. Many other lead systems are currently used in vectorcardiography, and a comparative study of their various theoretic and practical merits will be published subsequently.

As shown, the three vectorcardiograph leads (vertical, horizontal, and anterior-posterior) from the patient are connected to separate amplifiers. The amplifiers were designed and built in our laboratory, and their response has been shown to be linear over a frequency range of 0.5 to 150 cycles per second. Their response to a continuous 1.0 mv. direct current signal shows less than 3 per cent decrement 0.2 second after the introduction of the signal, and falls to 33 per cent of the original response in 2.7 seconds. These amplifiers together with the direct-coupled amplifiers of the Dumont 304-H cathode ray oscilloscope give a maximum sensitivity of 10 inches per millivolt on the face of the oscilloscope.

The outputs of these amplifiers (horizontal =

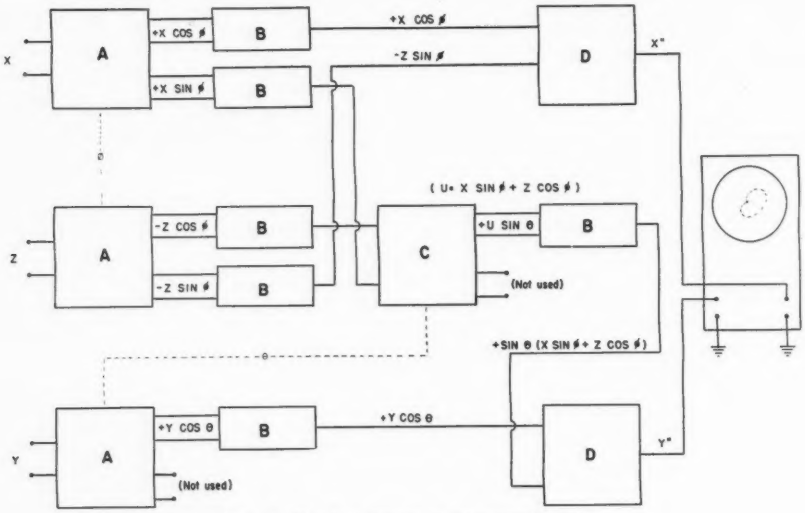

FIG. 3. Block diagram of panoramic unit

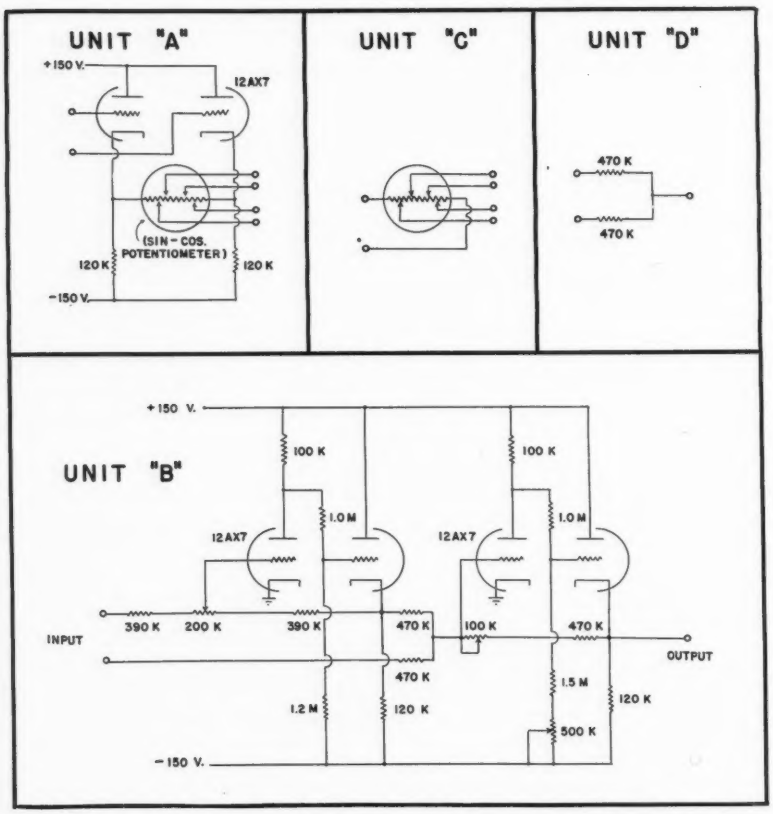

FIG. 4. Schematic diagram of the panoramic unit components shown in figure 3

x vertical = y, anterior-posterior = z) are fed to the circuits of the panoramic unit, shown in figures 3 and 4. This unit is essentially a calculator, which carries out addition and subtraction by unity amplifiers,[9] and performs the mathematic transformations[8]:

$$E_{x''} = E_x \cos \phi - E_z \sin \phi$$

$$E_{y''} = E_y \cos \theta + \sin \theta (E_x \sin \phi - E_z \cos \phi)$$

The single-ended outputs of the panoramic unit (x'' and y'') are connected to the plates of a Dumont 304-H oscilloscope through its direct coupled amplifiers.

Vectocardiograms are photographed on 70 mm. photographic paper (Eastman Kodak Linagraph No. 1127), using a "Varitron" camera, Model E,* (not shown in fig. 2) with a Carl Zeiss Tessar f/3.5 lens. Time intervals in the vectorcardiograph loops are indicated by modulating the beam intensity so that the trace is blanked every 0.004 second for a period of 0.002 second. The timing signal is not a square wave, but is peaked by a capacitor, so that the dashes which make up the loops are wedge-shaped, and point in the direction of rotation.

Three plane projections of the vectorcardiogram are recorded consecutively: frontal, sagittal and transverse. The sagittal view which we use routinely is the view of the spatial vectorcardiogram from the patient's right side. The transverse view is recorded so that the patient's right side lies to the reader's left, and the patient's chest lies toward the bottom of the page.

The y'' output of the panoramic unit is also displayed on a second cathode ray oscilloscope, against a linear time sweep. This scope is used only as a monitor, and the y'' output is recorded on one channel of a Hathaway S-14 C oscillograph.† The outputs of the amplifiers are recorded on other channels of this oscillograph. The galvanometers used are Hathaway Type OC-2, and have an undamped natural frequency of 500 cycles per second. A paper speed of 50 mm. per second is used, and an independent timer registers time lines at intervals of 0.01 second, with heavier lines at 0.05 second and 0.10 second intervals.

To describe three-dimensional data some arbitrary conventions must be adopted, and the spatial coordinate system we have used is shown in figure 5. The zero axis in this system is at the line of intersection of the frontal and transverse planes, on the patient's left side. Position above or below the horizontal plane is termed "elevation" (θ), and is described by the angle between the transverse plane and a line connecting the nullpoint with the point being designated, in a plane perpendicular to the transverse plane. Angles above the horizontal are designated as negative, and those below as positive. Position dorsal or ventral to the frontal plane is termed "azimuth" (ϕ), and is described in terms of projection on the transverse plane. Axes lying anteriorly, that is, ventrally, are designated as positive, and those posteriorly as negative. An observer, for example, whose position was at elevation = 0 degrees, azimuth = +90 degrees would see the frontal plane vectorcardiogram.

Any view of the spatial vectorcardiogram can be displayed by adjustment of two controls on the panoramic unit, which are calibrated in terms of the elevation and azimuth of the observer. This is illustrated in figure 6. The first vectorcardiogram in the top line in this figure is the standard frontal view of the spatial vectorcardiogram. If we remain at the same elevation, and change the azimuth control through successive intervals such as the 30 degree intervals illustrated, the corresponding views

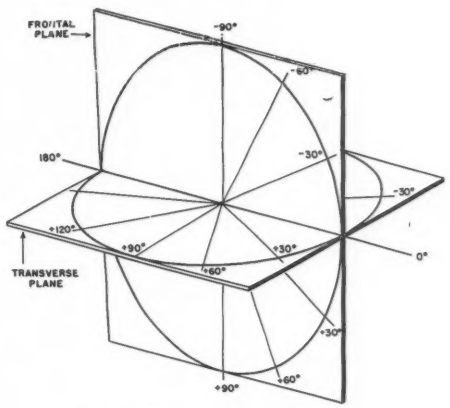

FIG. 5. Spatial coordinate system

of the vectorcardiogram appear on the oscilloscope, so that we move around toward the patient's right side until we see the sagittal view. In the lower line of this same figure, we start again with the frontal view, but this time maintain a constant azimuth and move to successively higher elevations until we look down on the spatial vectorcardiogram from above. In this way, by adjusting azimuth and elevation, we can view the spatial vectorcardiogram from any angle, making its characteristics from all aspects accessible without the construction of wire models or the use of stereoscopy.

In addition, the projection of the spatial vectorcardiogram along any single axis can be shown as a scalar electrocardiogram by using only the y'' output of the panoramic unit. As can be seen in figure 2, the vertical component of whatever loop appears on the first oscilloscope will appear as a scalar record on the second, and can at the same time be recorded permanently on one channel of the Hathaway oscil-

* Photographic Products Inc., Hollywood, Calif.
† Hathaway Instrument Company, Denver, Colo.

lograph. For example, when the frontal plane vectorcardiogram is being displayed on the first scope, the vertical vectorcardiograph lead will appear as a scalar electrocardiogram on the second. (The polarity of the electrocardiograph lead will be inverted in this case, since the frontal vectorcardiogram is recorded with positivity downward, or footward, on the scope; by rotating the elevation control 180 degrees the polarity can be made to conform with the electrocardiographic convention of recording

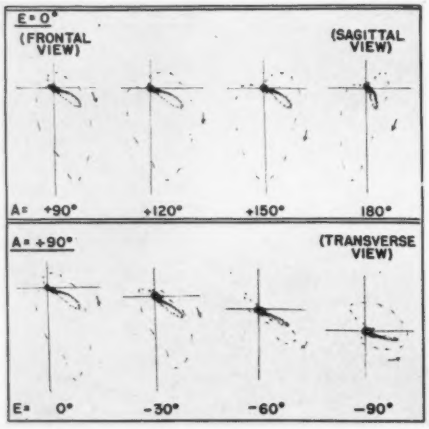

FIG. 6. Views of the spatial vectorcardiogram of a normal subject, showing how the panoramic vectorcardiograph can be used to display any projection of the spatial loops. The four vectorcardiograms in the upper line show views of the spatial vectorcardiogram from four different positions in the horizontal plane (elevation = 0 degrees). The view on the left is the usual frontal view (azimuth = +90 degrees). By changing the azimuth setting on the panoramic unit 30 degrees at a time, the observer moves around toward the patient's right side, finally reaching the sagittal view, at azimuth = 180 degrees in our coordinate system. In the lower line of records the first view is again the frontal view, but this time the azimuth is kept constant, and the elevation of the observer is changed. At elevation = −60 degrees the loops are seen almost on edge.

positivity by upward deflections.) Similarly, when the transverse view of the vectorcardiogram is shown on the first scope, the anterior-posterior component of the vectorcardiogram will appear on the second scope. It will be apparent that there is a difference of 90 degrees between the derived scalar lead and the position of the observer viewing the loop, so that it is convenient to have separate scales on the azimuth and elevation controls for these purposes.

In using the panoramic vectorcardiograph to predict from the vectorcardiogram the potential variations to be expected at various points on the body surface, the assumption is made that the electrical field of the heart in the body resembles that of a relatively small dipole source in a homogeneous conducting medium. Clearly, this is at best an approximation, but the point in question is whether it is a sufficiently close approximation to explain the form of the complexes recorded from the precordium and elsewhere, and if not, what discrepancies appear? This can be investigated by comparing complexes recorded by unipolar leads from the body surface, with scalar records corresponding to the same area, derived by the panoramic unit from the spatial vectorcardiogram. Comparisons of this kind can be only approximate since the location of the null-point in the body is not known with any exactness and we cannot therefore define a given point on the body accurately in terms of our coordinate system. We have tried to avoid this difficulty by taking electrocardiograms from a large number of points on the chest and back, and comparing them with a group of vectorcardiographic derivations corresponding to approximately the same area, rather than attempting a point-by-point comparison. A large number of axes through the vectorcardiograph were explored, using the cathode ray oscilloscope as a monitor; the coordinates at which complexes similar to the actual electrocardiograms occurred were noted, and the complexes recorded. The over-all *amplitude* of the actual and predicted complexes are not comparable, since the amplitude of all the predicted complexes were arbitrarily adjusted to approximately the same size.

RESULTS

Fifty-two patients with heart disease, including cases of myocardial infarction, bundle branch block, and ventricular "strain," have been studied, as well as six subjects with no evidence of heart disease. The results obtained can best be shown by describing three illustrative cases. In these three cases, as in all cases studied to date, the actual body surface leads and the appropriate scalar derivation from the vectorcardiogram resemble each other very

closely, provided the approximate position of the electrical nullpoint is taken into account.

Case 1. This patient was a white male, 21 years of age, with no evidence of cardiac or other disease. Figure 8 shows some of the electrocardiograms recorded from this subject, and scalar derivations from his vectorcardiogram corresponding to approximately the same area. The upper three lines of records in figure 8 are unipolar (V) leads taken at the three different transverse levels, *A*, *B*, and *C*, indicated in figure 7. The vertical alignment of these leads corresponds to the standard precordial positions and their counterparts on the right chest. Several features of this series of leads are of interest. First, at all three levels the R wave becomes larger and the S wave smaller as we go from the right side of the chest to the left, just as in the normal routine precordial leads. Second, along each vertical line, the R wave becomes larger and the S wave smaller as we move from the upper part of the chest downward. In other words the transitional complexes, in which R and S are roughly equal, are displaced further to the patient's right as we go downward from one level to the next. Third, at level *A* lead V_{6R} is a mirror image of lead V_6, and V_6 has the same form as standard lead I. This is not true at level *B* or *C*, and suggests that the electrical nullpoint lies near the transverse plane indicated by level *A*.

All of these characteristics are also found in the scalar vectorcardiograph derivations. The electrocardiograms from level *A* correspond quite closely to the derivations from the transverse vectorcardiogram (elevation = 0 degrees), as would be expected if the zero point were at this level. In comparing the vectorcardiograph derivations with leads at other levels it is important to realize that the leads taken at any one transverse level are not all at the same angle of elevation with respect to the nullpoint in our spatial coordinate system. This is due to the eccentricity of the nullpoint in the body, so that points along a given horizontal level on the body surface are not equidistant from it. If the nullpoint lies on the left side of the body, which seems probable, then leads on the left side of the chest will be at a greater angle below it than leads on the right side. At the horizontal level passing through the nullpoint this does not apply.

For this reason one would not expect all the vectorcardiograph derivations corresponding to electrocardiograph leads at levels *B* or *C* to be found at the same elevation settings, but would expect the greatest angles of elevation for leads on the left chest. This is borne out by the derivations shown in figure 8. To find the scalar vectorcardiograph derivation corresponding to V_6 at level *C*, for example, it is necessary to move down to elevation = +65 degrees, while the derivation corresponding to V_{6R} at this level appears at elevation = +50 degrees, and that corresponding to V_2 is at elevation = +30 degrees. Leads V_8, V_{8R}, and V_{ML}, taken at the angles of the scapulae and in the midline of the back, also have their counterpart in vectorcardiograph derivations, as shown at bottom right in figure 8.

In this case the P and T waves in the scalar vectorcardiograph derivations resemble those in the actual leads fairly closely. In many cases this is not true, as Jouve[5] and Duchosal[1] have pointed out, and it seems probable that the electrical nullpoint assumes a different position for each of the three electrical events represented by the P, QRS, and T deflections.

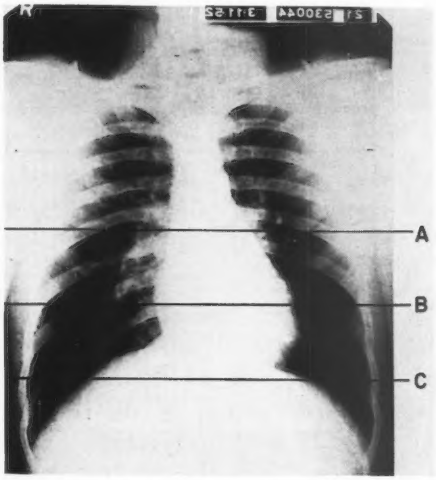

FIG. 7. Case 1. Chest x-ray film showing the three levels at which the unipolar electrocardiograms in the first three lines of figure 8 were taken.

Case 2. The records from this case, a 30 year old white female with classic signs and symptoms of mitral stenosis, are shown in figure 9. The vectorcardiogram shows changes frequently seen in this condition. The P loop is large and notched, and the frontal QRS loop is tilted far to the right. In the sagittal view the QRS is displaced toward the chest and in the transverse view the QRS loop rotates clockwise, which is almost never seen normally.

In the electrocardiogram, precordial leads V_{6R} to V_6, taken at the level of the fifth anterior intercostal space, show the pattern frequently seen in right ventricular strain. There is a large R wave in the right-sided leads, an RS in the midprecordials, and a large R with little or no S in the left-sided precordial leads. As others have pointed out,[1, 2, 5] this kind of QRS transition cannot be reconciled with the transverse vectorcardiogram, or indeed with any single plane through the spatial vectorcardiogram, since predominantly positive deflections appear on both sides of the chest. If, however, we record V_6 at higher levels, (fig. 9*E*), we find that at the level

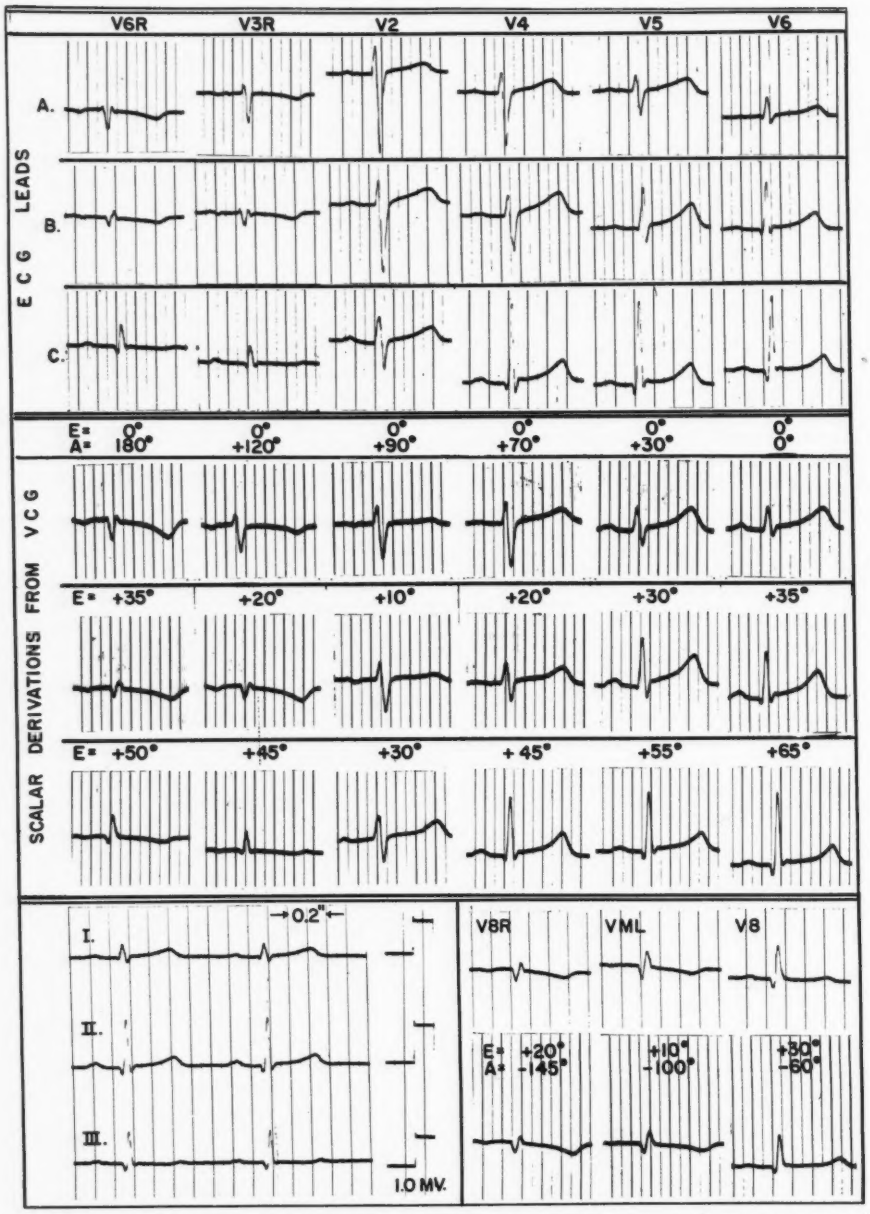

FIG. 8. Case 1. The records in the first three lines are unipolar (V) electrocardiograms taken at the levels indicated in figure 7. The next three lines show comparable scalar derivations from the spatial vectorcardiogram. The form of the complexes is very similar in the two sets of records. The over-all amplitude of the complexes is not comparable, since the scalar vectorcardiograph derivations were calculated as if all were equidistant from a central dipole. Standard electrocardiograph leads I, II, and III are shown lower left. The paper speed and standardization indicated apply also to the chest leads. In the lower right three unipolar electrocardiograms from the back are shown, again with comparable scalar vectorcardiograph derivations. V_S and V_{SR} were taken at the angles of the left and right scapulas, respectively, at level "*B*" (fig. 7). V_{ML} was taken in the posterior midline at the same level.

of the second anterior intercostal space it has the same form as lead I, suggesting that the electrical nullpoint lies at this relatively high level in the chest, just as in case 1. It seems probable, therefore, that these precordial leads were well below the level of the nullpoint, and should not be compared with the transverse plane vectorcardiogram. When we use the panoramic unit to record scalar vectorcardiograph derivations for angles below the nullpoint, we find the same QRS transition as in the precordial leads (fig. 9).

Case 3. This patient was a 40 year old white male who had shown clinical evidence of acute myocardial infarction six weeks before the records shown in figure 10 were made. According to the "semidirect" theory, the deep Q waves and inverted T waves in leads V_2 to V_6 would be regarded as local effects attributable to the proximity of the exploring electrode to the injured myocardium. The same deflections, however, are reproduced in scalar derivations from the spatial vectorcardiogram, although the vectorcardiogram was recorded by leads nowhere near the precordium.

Discussion

1. Precordial Leads and the Transverse Projection of the Spatial Vectorcardiogram

Discrepancies between the precordial electrocardiogram and the transverse vectorcardiogram have been reported by several investigators,[1, 2, 5] and have been interpreted in different ways. Duchosal[2] has offered the explanation that there is a continuous displacement of the nullpoint during the QRS complex. Although it seems probable on theoretic grounds that this does occur to some extent, the fact that the precordial leads do not usually lie in the same transverse plane as the nullpoint appears in our cases to be a much more important factor in producing these discrepancies. When this factor is taken into account, it is not necessary to assume a changing locus for the nullpoint during the QRS.

In many of our cases, as in the three illustrated, the QRS nullpoint appeared to lie much higher in the chest than the anatomic center of the ventricles, and the standard precordial positions were therefore below it. This is in accord with the observation frequently made in the routine reading of electrocardiograms, that lead V_6 does not have the same form as lead I, but more closely resembles lead II, or a lead along an axis between leads I and II. Similar findings have been reported by Jouve and his co-workers,[5] who state that the zero point in normal subjects is situated to the left of the midline, in a horizontal plane between the third and fifth rib, and that in cases of right ventricular hypertrophy it is higher in the chest.

From our preliminary observations in this regard it seems that there may be a correlation between the location of the nullpoint and the mean QRS axis. In the three cases illustrated, the mean QRS axis lies below the horizontal, and the nullpoint is relatively high in the chest. In left bundle branch block and left ventricular hypertrophy, where the mean QRS axis lies above the horizontal, the nullpoint in the few cases we have studied with this point in mind has been lower, at about the level of fifth anterior intercostal space. Further investigation of the position of the nullpoint in various cardiac abnormalities is indicated.

2. The "Semidirect" Hypothesis

The Wilson central terminal and unipolar V leads were introduced because it was thought desireable to know the "absolute" variations in potential (measured with reference to an "indifferent" point) at various points on the body.[10] Bipolar leads such as standard leads I, II, and III were considered to be "mixtures" of electrical information because they were measurements of the difference in potential between two points, both of which showed wide changes of potential during the cardiac cycle. Aside from the question of whether the potential variations of the central terminal are in fact negligible for practical purposes, the electrical information recorded by unipolar leads would be more useful than that recorded by bipolar leads only if the cardiac electrical field were grossly irregular, with preferential conduction pathways from certain parts of the heart to particular parts of the body surface. If, however, the field were approximately symmetric, like that of a simple dipole, then there would be no essential difference between unipolar and bipolar leads, provided the bipolar electrodes were equidistant from the source. The wave form recorded by either type of lead would depend on the axis of the lead in the

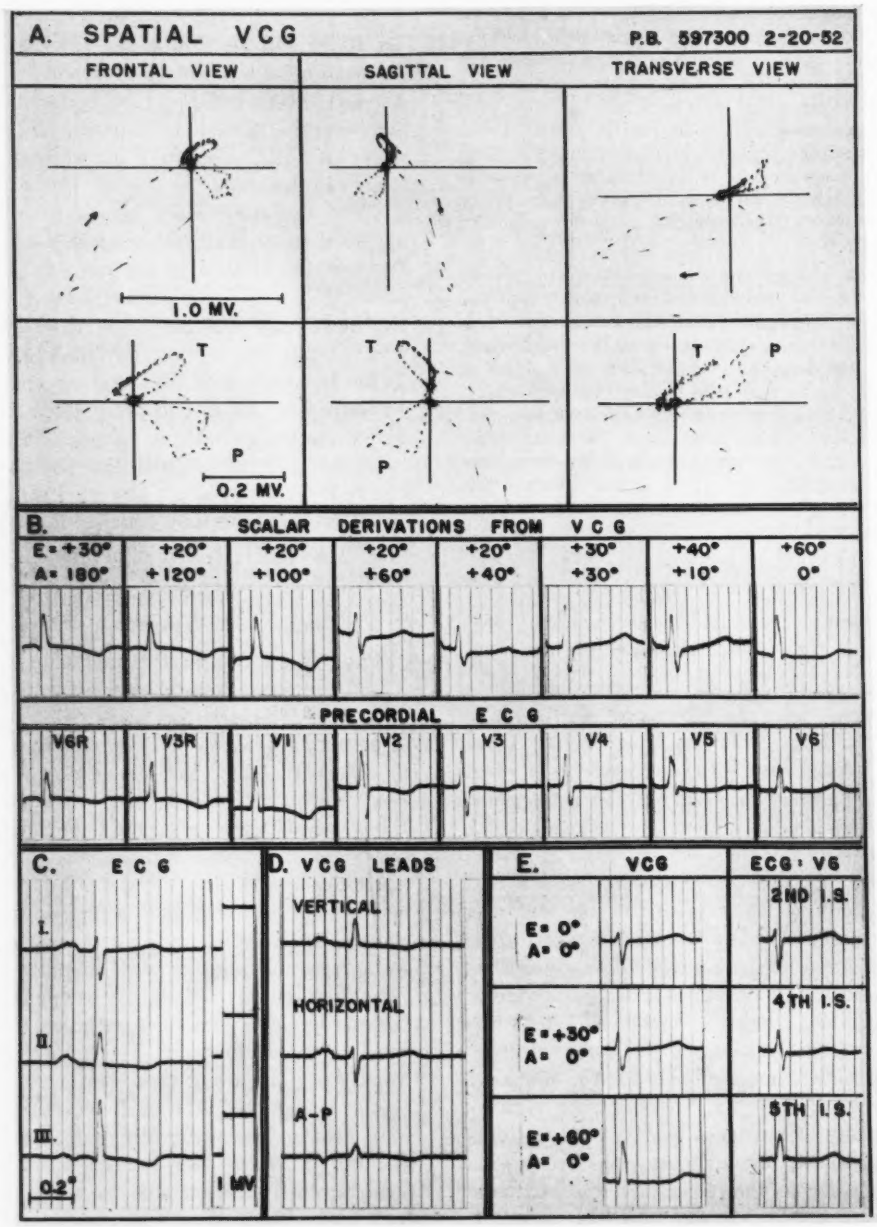

FIG. 9. Case 2. A 30 year old female with clinical evidence of rheumatic mitral stenosis. (*A*) Spatial vectorcardiogram. The details of the P and T loops are shown at higher amplification below each view. The sagittal view is shown as if viewed from the patient's right side. The transverse view is oriented so that the patient's right side lies to the reader's left, and the chest wall toward the bottom of the page. Arrows indicate direction of rotation of the QRS loop. The cathode ray beam is interrupted at intervals to provide a time scale, so that 4 milliseconds elapse from the beginning of one dash to the beginning of the next. (*B*) Comparison of unipolar precordial leads with scalar derivations from the vectorcardiogram. All precordial leads were taken at the level of the fifth anterior intercostal

electrical field, the axis of unipolar leads being the line from the exploring electrode to the electrical nullpoint.

In the cases illustrated, and in our other cases, it appears that the complexes in unipolar leads from the precordium or any other point on the body can be interpreted in terms of a relatively symmetric electrical field. The relative proximity of the exploring electrode

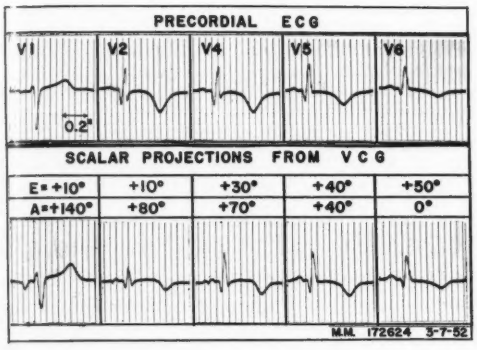

FIG. 10. Case 3. Unipolar precordial electrocardiogram and scalar projections of the spatial vectorcardiogram from a patient who had clinical evidence of acute myocardial infarction six weeks prior to this record. The characteristic Q and T waves appear in both sets of records, although the vectorcardiogram was recorded from leads distant from the precordium.

to one part of the myocardium seems to be comparatively unimportant in determining the general form of the complexes. The fact that the form of precordial and other unipolar leads can be predicted from a spatial vectorcardiogram which is recorded by leads at a distance from the heart, seems to us incompatible with the concept, found in many modern textbooks of electrocardiography, that the complexes in unipolar precordial leads represent the electrical activity of the nearest portion of the heart.

This concept has arisen from an interpretation, which we believe to be erroneous, of the experiments published by Wilson and his coworkers.[11] These investigators showed in dogs that the potential variations recorded by unipolar (V) leads at any point on the precordium were approximately the same as those recorded by direct unipolar leads from the underlying epicardium. From this they concluded that "... the potential variations of a precordial electrode are determined to a very large extent by the potential variations of the elements of ventricular surface nearest it."[12] This is somewhat misleading, for it implies that the electrical events in the nearest elements of the myocardium are the principal factor in determining the complexes recorded by unipolar epicardial or precordial leads. This was not the authors' intention, for they point out that even in direct epicardial unipolar leads the truly local effects are represented only by the "intrinsic deflection," and add "... although the excitation of the muscle in contact with the exploring electrode produces a much larger and much more sudden fluctuation in the potential of this electrode than the excitation of any equal mass of muscle at a greater distance from it, every unit of ventricular muscle, without exception, produces action currents which contribute to the form of these complexes."[12] Unquestionably, the contribution of each part of the myocardium must be inversely proportional to its distance from the exploring electrode; the problem is to identify, in the complexes recorded from the body surface, the local contribution. Our data indicate that the effects contributed locally must be very small, since the general form of the complexes is the same as if they were distant projections of a single dipole.

It might be supposed that the slurring and notching frequently seen in precordial leads

space. P waves have been omitted. (*C*) Standard electrocardiograph leads. (*D*) Leads used to record the vectorcardiogram. The lead system used consists of bipolar leads with a common electrode on the back of the right shoulder. (*E*) Comparison of three unipolar leads, taken in the left midaxillary line at different levels, with appropriate scalar derivations from the vectorcardiogram. At the level of the second anterior intercostal space the QRS complex has the configuration which the theory of "semidirect" leads regards as characteristic of the right ventricle, while at the level of the fifth intercostal space, its form is that said to occur in unipolar leads "facing" the left ventricle.[4] As can be seen in the scalar vectorcardiograph derivations, these deflections can equally well be explained as projections of the electrical activity of the whole heart.

recorded by instruments with good high-frequency response might be local effects, and would be absent from the vectorcardiogram. This has not proved to be true in our cases, for in all instances the same slurring and notching appeared in scalar vectorcardiograph derivations. This is consistent with the observations of Kossmann and his co-workers,[7] who found that notches in the complexes recorded by intracardiac leads corresponded to simultaneous notches or peaks in all precordial and extremity leads. It is of interest that in our cases the timing of the notches within the QRS complex was occasionally slightly different in the precordial lead and in the vectorcardiogram, and discrepancies of this kind need to be studied more closely.

3. Clinical Interpretation of Unipolar Leads

The clinical interpretation of unipolar precordial leads rests on empiric foundations which have been gradually built up from clinical and postmortem correlations. The theory that they are semidirect, or local, leads has been fitted into this empiric background without serious incompatibilities, but the validity of most current criteria for interpretation rests on empiric observations and does not depend on the validity of the "semidirect" hypothesis.* For this reason the demonstration that precordial leads actually represent summations of electrical activity in all parts of the heart, rather than predominantly local effects, would have little effect on their clinical interpretation.

In case 3, for example, the pattern in the precordial leads is that which has been shown empirically to occur when there is infarction of the anterior wall of the ventricles. We have learned to recognize the changes in the cardiac electrical field which infarcts in this location produce by the presence of characteristic Q waves and T waves in precordial leads, but it can be seen from the spatial vectorcardiogram and the scalar derivations from it that these electrical changes are not restricted to the precordium. The Q waves, therefore, are simply one aspect of the changes in the electrical field throughout the body, and cannot be regarded as a "view" of the electrically negative ventricular cavity through a "window" of necrotic myocardium.

The interpretation of the unipolar extremity leads, on the other hand, and their supposed advantages over bipolar leads, have been based largely on the semidirect hypothesis. Their use to determine anatomic rotation of the heart around various axes[4] is a pertinent example. It has been difficult to test the validity of this practice because there is no reliable method for determining anatomic rotation of the heart in vivo. However, strict adherence to the theory leads in some cases to most unusual conclusions, making it necessary, for example, to assume that the left ventricle lies to the right of the right ventricle.[6] Our results suggest that the unipolar extremity leads are predominantly influenced, not by the particular chamber they "face," but by the axis of the lead in the electrical field of the heart. In this respect, therefore, unipolar extremity leads offer no advantage over bipolar extremity leads.

Summary

1. A "panoramic vectorcardiograph" is described, which will present any desired view of the spatial vectorcardiogram on a cathode-ray oscilloscope. The viewpoint of the observer may be changed at will by adjusting two controls calibrated in terms of his azimuth and elevation with respect to the nullpoint of the vectorcardiogram. This instrument will also calculate and make scalar electrocardiograms representing projections of the spatial vectorcardiogram on any single axis.

2. This device eliminates some of the problems previously encountered in deriving scalar electrocardiograms from the spatial vecto-

* One exception is the measurement of the timing of the "intrinsicoid deflection" in precordial leads. In experimental work the intrinsic deflection recorded by contiguous bipolar electrodes in contact with the myocardium is a valid indication of the time of arrival of excitation, but the applicability of this concept to unipolar leads from the body surface is open to serious question. If the QRS complex in these leads represents a summation of events from all parts of the heart, then the peak of the R wave simply indicates the time at which this summation reaches a maximum positive value. It seems doubtful that this gives any useful information about the extent of the wave of depolarization at that instant.

cardiogram, since the necessary calculations are made automatically, and for any spatial axis.

3. In 58 subjects unipolar electrocardiograms recorded from the precordium and other points on the body surface showed a close resemblance to appropriate scalar derivations from the spatial vectorcardiogram. This was true even in cases of myocardial infarction, where the precordial leads showed changes previously thought to be "local effects" due to the proximity of the exploring electrode and the injured portion of myocardium.

4. Some of the previously reported discrepancies between precordial leads and the transverse vectorcardiogram can be shown to be due to the fact that the electrical nullpoint lies relatively high in the thorax, so that the precordial lead positions lie in a plane which cannot be compared directly with the transverse vectorcardiogram.

5. These results support the general hypothesis of Duchosal that for all body surface leads the electrical field of the heart approximates that of a single relatively small dipole in a homogeneous conducting medium. The form of the complexes in precordial and other unipolar leads appears to depend more on the axis of the lead in the cardiac electrical field than on preferential conduction from one part of the heart to the exploring electrode.

Acknowledgments

It is a pleasure to acknowledge the contributions of Mrs. R. A. Hess, who recorded and processed the vectorcardiograms and electrocardiograms in this work, of Mr. Thomas G. Arnold, who designed details of the computing circuits and intermediate amplifiers, of Mr. John Harper, who constructed the electronic equipment, and of Mr. L. W. Reynolds, who built the coupled mounts of the sine-cosine controls.

Sumario Español

A la extensión que tomas precordiales y otras unipolares son influenciadas por la proximidad del electrodo explorador a una porción o la otra del corazón es tópico de considerable debate. Una aproximación al problema es determinar cuán cerca se pueden predecir las tomas precordiales por medio de vectorcardiogramas espaciales registrados con tomas relativamente remotas del corazón. El vectorcardiografo panorámico ya citado provee un método conveniente de demostrar esto, puesto que automáticamente registra derivaciones númericas del vectorcardiograma para cualquier eje espacial. Los resultados indican que los efectos locales no son el factor predominante en la determinación de la forma de los complejos precordiales.

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Studies of the Spatial Vectorcardiogram in Normal Man

By G. E. Burch, M.D., J. A. Abildskov, M.D., and J. A. Cronvich, M.S.

The spatial vectorcardiograms of 75 normal subjects have been studied and some features of these records are described. The QRS sÊ and T sÊ-loops were found to have only two basic spatial configurations but with a variety of orientations thus giving widely different planar projections and in part accounting for the wide range of normal electrocardiograms. The significance of this and other findings is discussed and certain concepts pertinent to the study of the vectorcardiogram are presented.

THE CONCEPT of vectorcardiography is not a new one.[1-9] Increasing interest in this technic is evidenced by the number of papers and monographs recently published.[10-13] This interest is stimulated particularly by the hope that spatial vectorcardiography will have clinical applications exceeding those of conventional electrocardiography. At present the many variations in methods of recording and analyzing vectorcardiograms create difficulties in comparing data from different laboratories. It is desirable that these procedures be standardized as early as possible to foster more general application of the vectorcardiogram.

Despite this lack of uniformity, it is considered that a report of our experience with the vectorcardiogram of normal adults and of certain concepts which have evolved during the past several years of study of the vectorcardiogram in this laboratory would be of some interest. It should be realized that, since vectorcardiography is still an experimental method with no standardized reference system or nomenclature and since this series of subjects is small, the results convey merely a general impression of the normal as recorded with the tetrahedral reference system of Wilson and associates[14] and should by no means be construed as a complete description of all the possible variations that might be encountered in normal people under many different physiologic circumstances. This report is also intended to present certain aspects of the general problem of vectorcardiography, including a discussion of the reference system employed in these studies.

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Materials and Methods

Studies were made on 71 male and four female medical students between the ages of 22 and 33 years who had no evidence of cardiovascular disease. A teleoroentgenogram of the chest was obtained for each subject, and careful fluoroscopic examination of selected subjects was performed to determine, insofar as possible, cardiac position.

Electrocardiograms, including the standard limb leads, unipolar limb leads, precordial leads V_1 through V_6, and a unipolar lead from an electrode placed 3 cm. to the left of the seventh dorsal vertebra (V_B), were obtained for each subject when the vectorcardiogram was recorded. For the purpose of evaluating the efficacy of vector analysis from electrocardiograms, leads I and V_F and leads V_B and V_F, representing the components of the frontal and sagittal projections of the vectorcardiogram, were recorded simultaneously at the conventional electrocardiographic film speed of 25 mm. per second and at a film speed of 50 mm. per second. Leads I and III, II and III, and V_R and V_L were also recorded simultaneously at conventional film speed.

Spatial vectorcardiograms (sVCG) were obtained with the use of the equilateral tetrahedron as a reference system. In this system the Einthoven triangle constitutes the frontal plane, and the remaining apex of the tetrahedron is represented by a point on the back 3 cm. to the left of the seventh

dorsal vertebra. Frontal and sagittal plane projections of the vectorcardiogram were photographed simultaneously from two single beam cathode-ray oscilloscopes. The frontal plane projection was obtained by connecting the right and left arm electrodes to the horizontal-deflecting plates of the cathode-ray tube and by connecting a Wilson central terminal and the left leg electrode to the vertical-deflecting plates. Connections were such that relative positivity of the left arm produced a deflection of the beam to the left (the observer's right), and relative positivity of the left leg produced a downward deflection.

In the sagittal plane, horizontal deflections were obtained from a Wilson central terminal and the back electrode, and vertical deflections from a central terminal and the left leg. Relative positivity of the back electrode resulted in movement of the electron beam to the right as viewed by the observer facing the sagittal plane from the left, and relative positivity of the foot resulted in a downward deflection.

Standardizing factors, which are necessary because the potential differences are scalar quantities being treated as vectors, were such that 1 mv. introduced into the vertical-deflecting circuit of either oscilloscope produced a deflection of $1\frac{7}{10}$ inches and, when introduced into the horizontal-deflecting circuits, produced a deflection of 1 inch on the oscilloscope used to record the frontal projection and $1\frac{3}{10}$ inches on the oscilloscope used to record the sagittal projection.[15]

The projections of the vectorcardiogram on the right, left and superior planes of the tetrahedron were obtained by selecting the proper electrode combinations and proper central terminal and employing appropriate standardizing factors. Each of these plane projections was recorded simultaneously with another plane projection sagittal to it and each pair of planes was treated as was the frontal plane and the plane sagittal to it. In addition, stereoscopic views of the spatial vectorcardiograms from the front, the right, the left and the superior planes of the tetrahedron were obtained by the use of a technic previously described.[16-17] In all, eight plane projections and four stereoscopic views of the spatial vectorcardiogram were obtained for each subject. Frontal and left sagittal projections and frontal stereoscopic views were recorded, both with amplification sufficient to show all components of the vectorcardiogram and with higher amplification to show details of the P, QRS, and T sÊ-loops near the isoelectric point. Time was indicated in all records by interrupting the oscilloscopic trace 600 times per second. Finally, three-dimensional wire models representing each spatial vectorcardiogram were constructed to conform to all of the plane projections recorded.

Each of the plane projections, the stereoscopic photographs and the models was inspected, and the contour of the QRS and T sÊ-loops, their relation to each other, and the directions of rotation were noted. The "axis" or the "maximal vector" of the QRS and T sÊ-loops, which is indicated by a straight line drawn from the origin of the respective loop to its most distant point, was measured in millivolts in the frontal and sagittal projections. Their position in a triaxial reference frame applied to these planes was also noted. In the case of the left sagittal plane, the ± 180 degree axis of the triaxial reference system was placed anteriorly. In addition, the maximal extent of the left sagittal plane projection posterior to the isoelectric point was measured in millivolts.

Rotations of the QRS and T sÊ-loops about their maximal longitudinal axes were defined in the following manner. The equilateral tetrahedron is visualized with its frontal plane vertical. A line is drawn horizontally through the terminus of the maximal vector and perpendicular to it. Whenever the vector is vertical, the line must also be parallel with the lead I axis of the tetrahedron. This line is considered to be the zero axis of a triaxial reference system whose origin coincides with the terminus of the maximal vector. The triaxial reference system is perpendicular to the maximal vector, and its zero axis lies to the right of an observer viewing the vector from its terminus. In practice, the loop is visualized with the terminus of the maximal vector facing the observer, and the position of the ascending and descending limbs in the triaxial reference system is noted.

Because of reports indicating that spatial vectorcardiograms can be utilized to predict the form of the precordial leads [8, 13] or that some characteristics of the spatial vectors can be inferred from the precordial leads,[18] 63 of the records in which the superior projection was technically satisfactory were subjected to such analysis. This was carried out by marking the approximate anatomic position of the six conventional precordial electrode sites on a diagrammatic cross section of the human chest. Each of these points was connected by a straight line to a point at the center of the chest, as shown in figure 1*A*. Perpendiculars were then drawn to each of the lines, as shown for V_1 in figure 1*B*. The isoelectric point of the superior projection of the vectorcardiograms was placed at the point of intersection of the lines shown in figure 1*B*. By this technic, the predicted polarity of the deflections in a given lead is indicated at any moment by the side of the line on which that portion of the vectorcardiogram lies. A similar analysis was carried out in 25 instances in which the horizontal plane projection of the spatial vectorcardiogram was recorded by means of the cuboidal system of electrode placement.[13] It is realized that the superior plane and the horizontal plane of the cuboidal reference system do not coincide with each other or with the plane or planes defined by the precordial leads.

Results

The difficulty of describing three-dimensional records of variable form is obvious. Some previous publications from this laboratory have partially avoided this difficulty by including two or more plane projections of each of the vectorcardiograms being described.[19,20] Since the larger number of records forming the basis of the present report makes it impractical to illustrate each, stereoscopic records have been selected to demonstrate the more common variations in form and orientation of the normal vectorcardiogram. These records, when viewed from a distance of 5 to 10 inches with a card placed between the two projections, give the observer a single stereoscopic image.

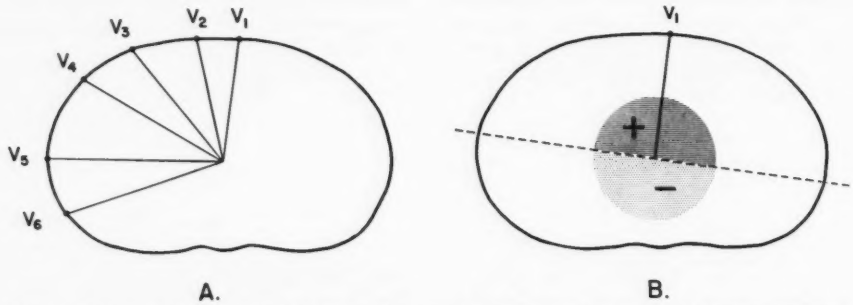


FIG. 1. Relation of precordial leads to the superior plane projection of the vectorcardiogram. (*A*) The approximate anatomic location of the precordial leads in a transverse plane of the body. (*B*) Relation of V_1 to the superior or horizontal plane projection of the spatial vectorcardiogram. Portions of the vectorcardiogram located anteriorly to the perpendicular (interrupted line) to V_1 indicate a positive deflection and portions located posteriorly to this perpendicular a negative deflection in lead V_1 of the electrocardiogram.

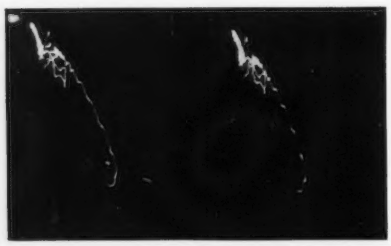


FIG. 2. Stereoscopic frontal view of a representative normal P sÊ-loop. The T sÊ-loop and a portion of the QRS sÊ-loop are also shown.

The P sÊ-Loop

With present methods of recording, the P sÊ-Loop is sometimes obscured by a halo due to slight movement of the cathode-ray beam during electrical diastole or is distorted by muscle tremor or by electrical interference. Such distortion is of greater significance in the case of the small P sÊ-loop than in the case of the larger QRS and T sÊ-loops. For these reasons, a detailed study of the normal P sÊ-loop was not attempted at this time. Certain general features of the normal P sÊ-loop were apparent, however.

The most commonly encountered form and orientation of the P sÊ-loop is illustrated by the stereoscopic photograph in figure 2. As demonstrated in this figure, the axis of the P sÊ-loop was usually directed downward, forward and to the left. Characteristically, one or more relatively large serrations were present in the contour of the loop. In most of the spatial vectorcardiograms, the P sÊ-loop was located posterior to the QRS sÊ- and T sÊ-loops.

The QRS sÊ-Loop

At the beginning of these observations inspection of the plane projections seemed to indicate considerable intrinsic variation in contour among the QRS sÊ-loops of this group of normal subjects. The extensive variations were comparable to those of the QRS complex of normal electrocardiograms. However, continued study of the stereoscopic views and the three-dimensional models modified this view. From these records it

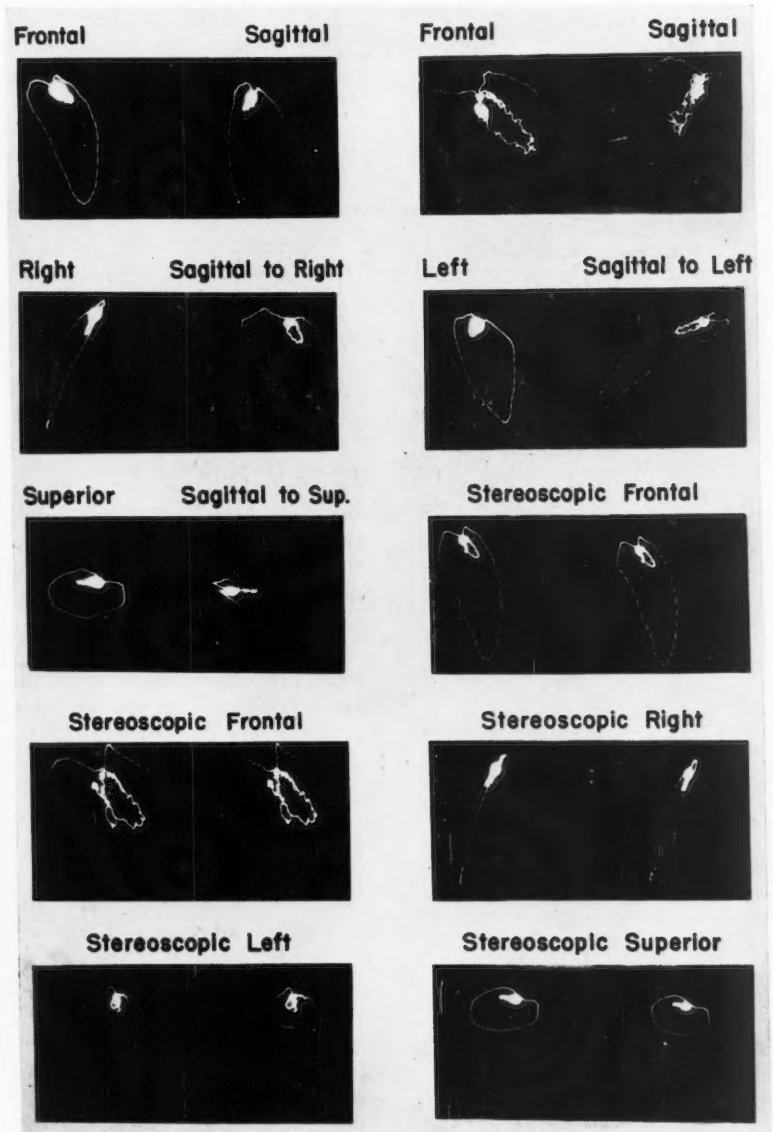


FIG. 3. Representative normal "type 1" QRS sÊ-loop. The eight plane projections and four stereoscopic views of the spatial vectorcardiogram as obtained on each of the subjects studied are shown. (See text for details.)

appeared that, aside from detailed variations, all QRS sÊ-loops in this series could be described as variants in spatial position of two basic patterns. This prompted the description of these QRS sÊ-loops and the T sÊ-loops under the headings of types 1 and 2.

Type 1

Sixty-six of the 75 records studied could be described as spatial positional variants of a pattern which is illustrated by the vectorcardiogram shown in figure 3. The eight plane and four stereoscopic views, such as were

obtained for each subject, are shown in this figure for a representative subject. The spatial orientation of the vectorcardiogram can be most easily appreciated by inspecting the frontal stereoscopic view according to the directions previously given. The impression obtained of the three-dimensional form and orientation of the record may then be compared with the actual projection in planes other than the frontal. For example, the impression gained from the stereoscopic view concerning the extent of displacement of the various portions of the vectorcardiogram, anterior and posterior to the isoelectric spot, may be checked in the left sagittal projection.

(a) *General Characteristics.* In general, the QRS sÊ-loops of type 1 were elliptoid figures whose widths were approximately one-third of their respective lengths. For the most part the contours were smooth, with no sudden changes in direction. The loop was traced on the screen of the oscilloscope relatively slowly for a short distance near the origin, which represented up to about one-third of the QRS interval, faster through the major portion of the record containing the vectors of greatest magnitude, and slowly again near the terminus, which again represented up to about one-third of the QRS interval. The direction and magnitude of the maximal QRS vectors in the frontal and left sagittal projections and the maximal extent of the QRS posterior to the isoelectric point are summarized in table 1.

TABLE 1.—*Summary of Measurements in Type I, QRS sÊ-Loops*

	Maximal Vector in Frontal Plane				Maximal Vector in Sagittal Plane				Posterior Extent (MV.)
	QRS		T		QRS		T		
	Angle	Length	Angle	Length	Angle	Length	Angle	Length	
Minimal	+20	0.31	0	0.10	+66	0.21	+77	0.05	0
Maximal	+89	1.73	+84	0.56	+129	1.47	+144	0.52	0.42
Average	+66	0.99	+46	0.28	+107	0.87	+124	0.23	0.15

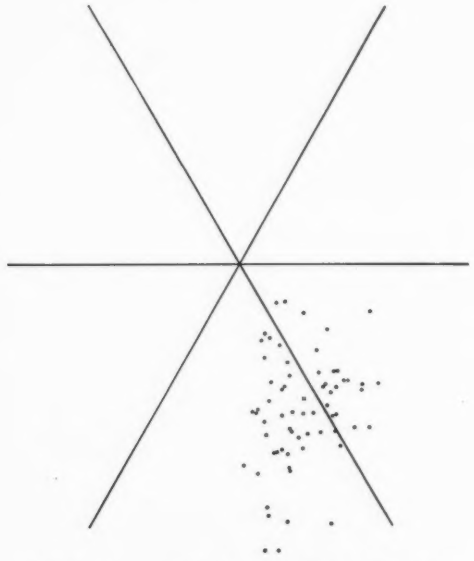


FIG. 4. Magnitude and direction of maximal QRS vectors in the frontal plane.

(b) *Variable Characteristics.* The records of type 1 differed chiefly as regards orientation about their anteroposterior, transverse and longitudinal axes. These axes may be defined as follows: (1) The *anteroposterior axis* is normal to the frontal plane and passes through the isoelectric point. (2) The *transverse axis* is normal to the anteroposterior axis and transverse to the body and passes through the isoelectric point. (3) The *longitudinal axis* of the respective sÊ-loops is represented by the maximal instantaneous mean electrical axis of the loop.

1. Orientation about Anteroposterior Axis: The variations in position about the anteroposterior axis are illustrated by figure 4, in which the magnitude and direction of the maximal QRS vectors in the frontal plane are shown for all 66 type 1 QRS sÊ-loops which were analyzed. It should be recognized that although the magnitude and direction of a single vector have only limited meaning, they

an be used to indicate the approximate orientation of records of essentially similar orm. In the frontal plane the direction of the naximal vector varied between +20 and +89 legrees.

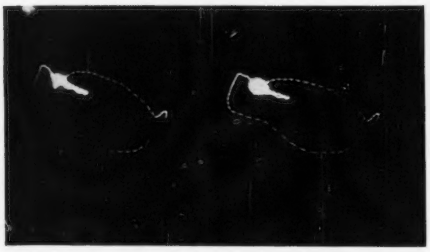


FIG. 5. Frontal stereoscopic view of a spatial vectorcardiogram with a "type 1" QRS sÊ-loop oriented horizontally about its anteroposterior axis.

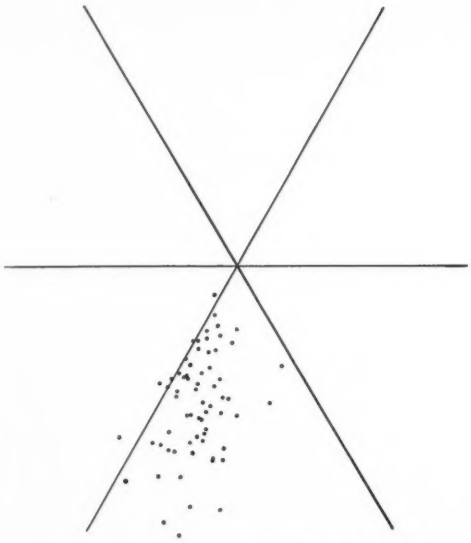


FIG. 6. Magnitude and direction of maximal QRS vectors in the sagittal plane.

Figure 5 shows a frontal stereoscopic view of a vectorcardiogram in which the QRS sÊ-loop is essentially similar in contour to that shown in figure 3 but which differs by being oriented more horizontally about the anteroposterior axis.

2. Orientation about the Transverse Axis: Variations in position about the transverse axis are illustrated by figure 6, which shows the

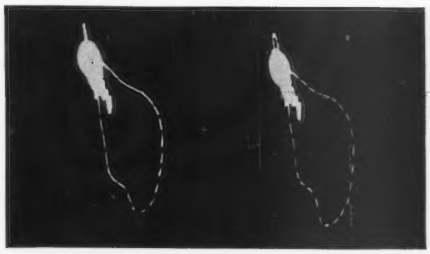


FIG. 7. Frontal stereoscopic view of a spatial vectorcardiogram with a "type 1" QRS sÊ-loop rotated posteriorly about its transverse axis.

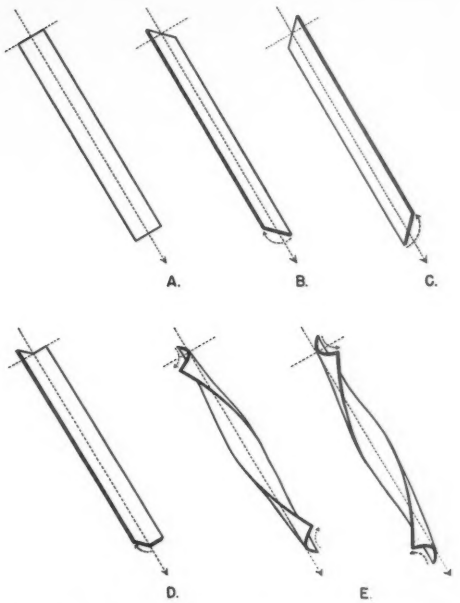


FIG. 8. Diagrammatic representation of the main types of orientation of the QRS sÊ- and T sÊ-loops about their longitudinal axes encountered in the spatial vectorcardiograms of 75 normal subjects. The number of spatial vectorcardiograms encountered with each of the orientations shown was as follows: (*A*) 13 "type 1" QRS sÊ-loops, 10 T sÊ-loops associated with "type 1" QRS sÊ-loops. (*B*) 33 "type 1" QRS sÊ-loops, 36 T sÊ-loops associated with "type 1" QRS sÊ-loops, and four T sÊ-loops associated with "type 2" QRS sÊ-loops. (*C*) Three "type 1" QRS sÊ-loops, seven T sÊ-loops associated with "type 1" QRS sÊ-loops and two T sÊ-loops associated with "type 2" QRS sÊ-loops. (*D*) Two "type 1" QRS sÊ-loops. (*E*) 15 "type 1" QRS sÊ loops, one T sÊ-loop associated with a "type 1" QRS sÊ-loop, and one T sÊ-loop associated with a "type 2" QRS sÊ-loop.

magnitude and direction of the maximal QRS vectors in the left sagittal plane for all 66 QRS sÊ-loops. The extremes were +66 and +129 degrees. Figure 7 shows a frontal stereo-

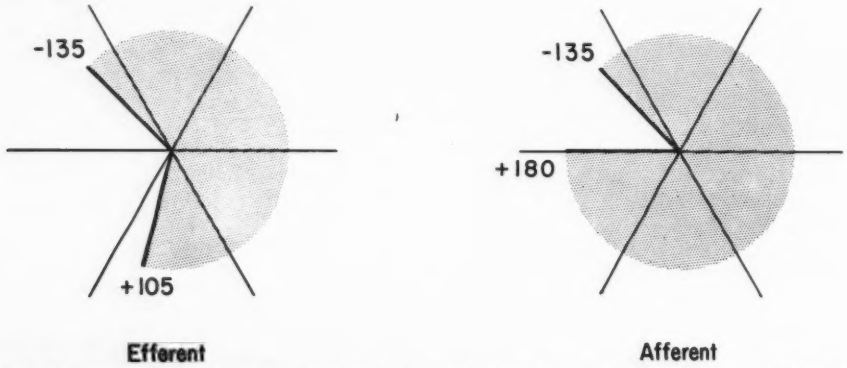
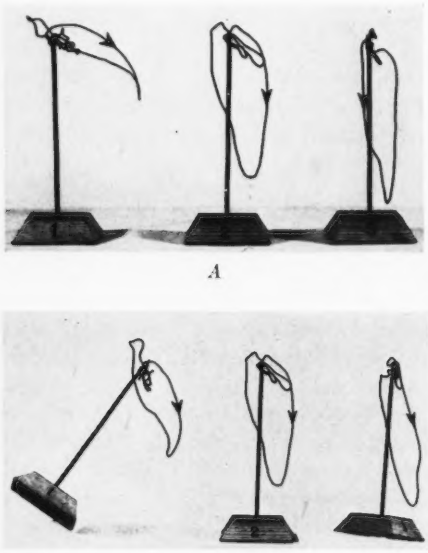


FIG. 9. Range of orientation of afferent and efferent limbs about the longitudinal axis of the QRS sÊ-loop.

FIG. 10. Frontal stereoscopic view of a spatial vectorcardiogram with a "type 1" QRS sÊ-loop rotated in a counterclockwise direction about its longitudinal axis with respect to the usual normal record.

scopic view of a vectorcardiogram whose QRS sÊ-component is again similar in contour to that shown in figure 3 but which is oriented differently about the transverse axis, being rotated posteriorly with respect to the usual normal record.

3. Orientation about the Longitudinal Axis: Figure 8 diagrammatically summarizes the variations in orientation about the longitudinal axis which were encountered in this series of records. In this figure a paper strip is intended to represent the QRS sÊ- or the T sÊ-loops. Thirteen QRS sÊ-loops were oriented as shown in A, 33 of the QRS sÊ-loops had varying degrees of rotation of the type shown in B, and three were oriented as shown in C. Two records showed different degrees of rotation of the ascending and descending limbs of the QRS sÊ-loop as shown in D. In 15 records two or more portions of the QRS sÊ-loops were



A

B

FIG. 11. (*A*) Models of three spatial vectorcardiograms constructed from planar projections. (*B*) Same models oriented to show their essential similarity of form.

oriented differently about the longitudinal axis, as is illustrated in E. When viewed from the terminus of the maximal QRS vector, the position of the efferent limbs in a triaxial

reference system, placed as described under "Methods," varied between −135 and +105 degrees. The position of the afferent limbs, similarly viewed, varied between +180 and −135 degrees. The range in orientation of the efferent and afferent limbs is shown diagrammatically in figure 9. Figure 10 depicts a QRS sÊ-loop again similar in form to that shown in figure 3 but rotated counterclockwise about its longitudinal axis in contrast to the usual normal record.

TABLE 2.—*Summary of Measurements in Type II, QRS sÊ-Loops*

	Maximal Vector in Frontal Plane				Maximal Vector in Sagittal Plane				Posterior Extent (mv.)
	QRS		T		QRS		T		
	Angle	Length (mv.)	Angle	Length (mv.)	Angle	Length (mv.)	Angle	Length (mv.)	
Minimal	+37	0.36	+30	0.12	−80	0.31	+113	0.10	0.31
Maximal	+116	0.84	+65	0.47	+117	0.73	+150	0.42	0.62
Average	+53	0.63	+45	0.28	+31	0.53	+126	0.25	0.42

Direction of Inscription. In 63 subjects the QRS sÊ-loop was inscribed in a clockwise direction in the frontal and in a counterclockwise direction in the left sagittal projection. In one subject the orientation of the QRS sÊ-loop was such that it was inscribed in a counterclockwise direction in both frontal and left sagittal projections, and in two subjects the QRS sÊ-loop was traced in a counterclockwise direction in the frontal and a clockwise direction in the left sagittal projection. The direction in which the QRS sÊ-loops were inscribed in the plane projections was influenced by orientation of the sÊ-loop about the anteroposterior, transverse, and longitudinal axes and not by differences in the general form of the loops. This is illustrated in figure 11, which shows three models constructed to conform to the plane projections of three different QRS sÊ-loops. In *A*, the models are shown in frontal view as they appeared on the screen of the oscilloscope as frontal projections of the sÊ-loops. When viewed from the front, the QRS sÊ-loops appear to be extremely different. Model 2 possesses the most common orientation of the QRS sÊ-loop and differs from model 1 mainly in its orientation about the anteroposterior axis. Model 3, which is traced counterclockwise in its frontal projection, is oriented differently in space, in this case mainly about the longitudinal and transverse axes. In figure *B* the same models are oriented differently to show that they are grossly similar in form. The apparent differences shown in figure 11*A* were due mainly to differences in position of the QRS sÊ-loops.

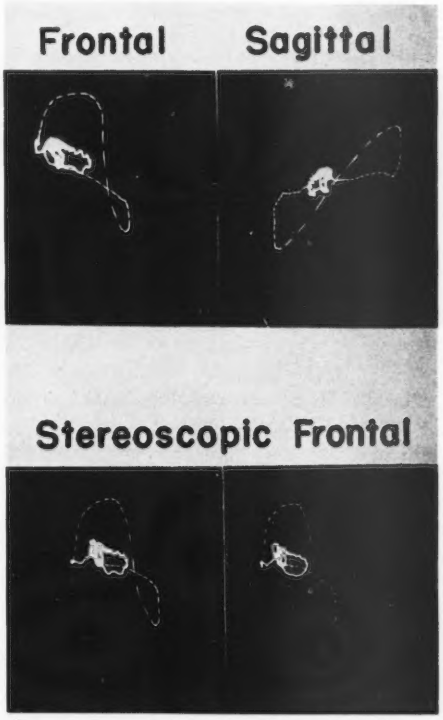


FIG. 12. Frontal, left sagittal, and frontal stereoscopic views of a representative normal "type 2" QRS sÊ-loop.

Type 2

Contour. Nine QRS sÊ-loops could not be conveniently considered with the 66 just described. These records were essentially similar in form and were characterized by having a greater area enclosed by the portion of the QRS sÊ-loop behind the isoelectric point than did the records of the type 1 pattern. In some subjects this resulted in a maximal QRS vector directed into the first or second sextants of the triaxial reference system and directed posteriorly in the left sagittal projection. A summary of the measurements of length and direction of the maximal QRS vectors in frontal and left sagittal projections and of the extent of the QRS loop behind the isoelectric point is presented in table 2.

Like the records of type 1, these QRS sÊ-loops were essentially smooth in contour. Unlike the QRS sÊ-loops of type 1, they did not enclose narrow ellipse-like areas but wider areas which in some records approached a circular form. In all records in this group the width of the QRS sÊ-loop was one-half or more of the length.

Orientation. Because of the tendency of these QRS sÊ-loops to enclose roughly circular areas, the position of the maximal QRS vector is of less value in indicating orientation. The initial portion of all records, however, enclosed an area in the sixth or in the fifth and sixth sextants of the triaxial reference system in the frontal plane and in front of the isoelectric point in the sagittal plane. The terminus of all records enclosed an area in the first and second sextants of the triaxial reference system and located behind the isoelectric point.

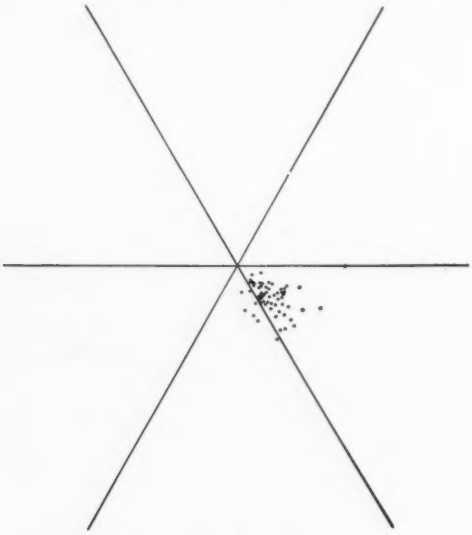


FIG. 13. Magnitude and direction of maximal T vectors in the frontal plane. The data illustrated in this scatter diagram were obtained from the T sÊ-loops associated with "type 1" QRS sÊ-loops.

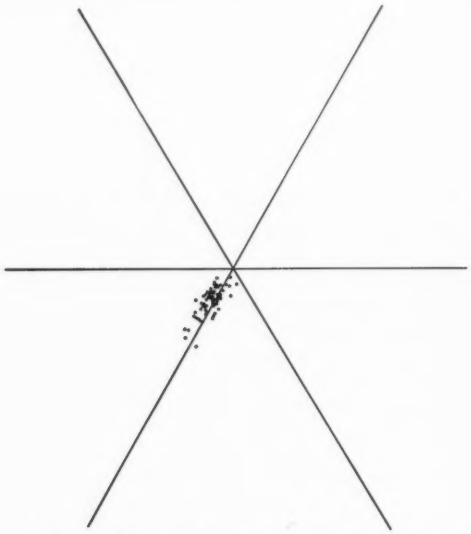


FIG. 14. Magnitude and direction of maximal T vectors in the sagittal plane. The data illustrated in this scatter diagram were obtained from the T sÊ-loops associated with "type 1" QRS sÊ-loops.

All of these loops tended to enclose single plane areas, the upper surface of which in six records was directed toward the left shoulder of the Einthoven triangle, in two records was directed toward the right shoulder, and in one record was essentially perpendicular to the frontal plane. A frontal stereoscopic view of a record typical of those of type 2 is shown in figure 12.

The T sÊ-loop

Because of the known influence of ventricular depolarization on the order of repolariza-

tion, the respective T sÊ-loops of the records divided into types 1 and 2 on the basis of similarity of the QRS sÊ-loops will be described separately.

The T sÊ-Loops Associated with Type 1 QRS sÊ-Loops

The most common form of the T sÊ-loop is a narrow elliptoid figure which is traced more slowly in its efferent than in its afferent portion. A frontal stereoscopic view of a representative normal T sÊ-loop is shown in figure 3. A summary of the measurements obtained is included in table 1.

Orientation about the Anteroposterior Axis. The direction of the maximal T vector varied between 0 and +84 degrees in the triaxial reference system of the frontal plane. Figure 13 shows the magnitude and direction of the maximal T vectors in the frontal plane.

Orientation about the Transverse Axis. Variations in position about the transverse axis are indicated in figure 14. Here the magnitude and direction of the maximal T vectors are shown in a triaxial reference system applied to the left sagittal plane. The direction varied between +77 and +144 degrees.

Orientation about the Longitudinal Axis. This will be described by reference to figure 8. Ten of the T sÊ-loops were oriented as shown in figure 8*A*, 36 as shown in *B*, seven as shown in *C*, and one as shown in *E*. Twelve records were not considered technically satisfactory for this part of the study.

The T sÊ-Loops Associated with Type 2 QRS sÊ-Loops

A summary of the magnitude and direction of the maximal T vectors in the frontal and sagittal projections is included in table 2. In form, the T sÊ-loops of six of the nine subjects included in this group were narrow elliptoid figures similar to those found in type 1. In four subjects the T sÊ-loops presented a different appearance, enclosing as did the QRS sÊ-loops almost circular areas. Whereas the T sÊ-loops of all subjects included in type 1 had widths of less than one-third of their length, the widths of the T sÊ-loops of these subjects were one-half or more of their length

Orientation. Although the spatial orientation of the T sÊ-loops of type 2 was largely within the limits defined for type 1, the variations were not as extreme. In the frontal plane, axes lay between +30 and +65 degrees and in the left sagittal plane between +113 and +150 degrees. Orientation about the longitudinal axis was likewise within the limits found for type 1. Two T sÊ-loops were oriented as shown in figure 8*A*, four as shown in *B*, two as shown in *C*, and one as shown in *E*.

The Junction

In 11 records the junction between the QRS sÊ-loop and the T sÊ-loop was displaced with reference to the isopotential point. A stereoscopic view of a record with this characteristic is shown in figure 15. A quantitative study of the position and magnitude of displacement of the junction was not attempted for the same reasons that a detailed study of the P sÊ-loop was not carried out. However, it should be mentioned that, when discernible, displacements varied in space and were not confined to one plane projection.

FIG. 15. Frontal stereoscopic view of a normal record showing displacement of the junction, J.

Relation of the Spatial Vectorcardiogram to Precordial Leads

Sixty-three of the records were utilized as outlined under "Methods" to predict the form of the precordial electrocardiogram. Figure 16 shows the superior plane projection of a vectorcardiogram superimposed on the reference system used to indicate the precordial leads, the precordial leads predicted from this projection, and the precordial leads actually recorded from the same subject. Note that R′ waves are present in leads V_1 through V_4 which

were derived from the vectorcardiogram, but not in the precordial leads which were actually recorded. Detailed characteristics of form and magnitude were not successfully predicted in any of the records analyzed. In 19 subjects large S waves were predicted in the left-sided chest leads, whereas no such waves were present in the precordial leads actually recorded. In 10 subjects, large R′ waves were predicted in the precordial leads to the right of the transition zone, whereas no R′ waves were present in the recorded leads. Since this pattern is considered abnormal by conventional electrocardiographic criteria, the spatial vectorcardiogram as used in this analysis must be considered inadequate to predict the form of the precordial leads.

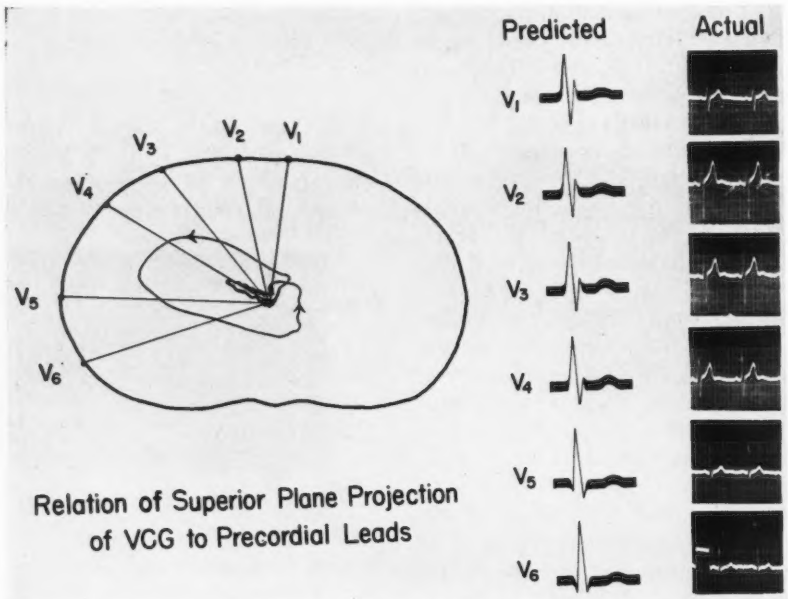


FIG. 16. Tracing of the superior planar projection of the QRS sÊ- and T sÊ-loops of a spatial vectorcardiogram shown in relation to the approximate anatomic location of the precordial leads. The precordial leads predicted from this view of the vectorcardiogram and the precordial leads actually recorded from the same subject are shown. Among the differences noted are the R′ waves present in leads V_1 through V_4 of the predicted precordial leads which are not present in the precordial leads actually recorded.

DISCUSSION

The spatial vectorcardiogram obtained with the equilateral tetrahedron as the reference frame is described for 75 normal medical students. Undoubtedly, these observations are of limited value to those employing other reference frames for recording the vectorcardiogram. In view of the great need for a single spatial reference frame for more or less general use in spatial vectorcardiography, it was considered that the equilateral tetrahedral reference system of Wilson and associates offered many advantages over the others and no disadvantage not inherent in all of them.

Among the *advantages* of the equilateral tetrahedral reference frame are: (1) Only *one more electrode position* needs to be added to the three already employed for recording the three standard leads. (2) All electrode positions are accurately and readily duplicated in serial recordings. (3) The electrodes are simple to apply and are easily retained in position. (4) Existing experience and knowledge obtained for the generally accepted equilateral triangle

of Einthoven can be readily applied to any or all the plane surfaces of the equilateral tetrahedron because these too are equilateral triangles.

The *disadvantages* common to all reference frames, including the equilateral tetrahedron, are due to the fact that: (1) The electrode positions are not truly remote. (2) The conducting medium of the body is not electrically homogeneous. (3) The electric dipole of the heart is not a single point source. (4) The electrode positions are not equidistant from the potential source.

Without entering into detailed analysis of the advantages and disadvantages of the various spatial reference frames, we are of the opinion that, although the equilateral tetrahedron is not ideal, it is superior to any others considered to date. It appears to us that it is advantageous to exploit as much knowledge as possible from electrocardiography, at least during the developmental phase of vectorcardiography, and the equilateral tetrahedron offers definite advantages in that regard.

During the early phases of these experimental studies, considerable difficulty was encountered in identification and interpretation of normal spatial vectorcardiograms. The normal plane projections were so variable that it was impossible to recognize with certainty a normal record and to differentiate a normal record from an abnormal one under study at the same time. This difficulty was overcome to a large extent when it was found that the normal spatial vectorcardiograms could be divided into two fundamental types and that the variations in configurations of the plane projections were merely the result of variations in spatial orientation of these two types of patterns. It then became a practice first to identify the fundamental type and then to proceed with the more detailed analyses and interpretations. It is of interest that Ashman[21] several years ago indicated that the normal spatial vectorcardiogram could be reduced to a mean pattern and that this pattern was useful in the application of the spatial vectorcardiogram to electrocardiography and to analyses of the spatial gradient, $s\hat{G}$.

It is not likely that only two normal patterns exist. More recent observations indicate a transitional pattern. Many more normal records under the influence of many physiologic states must be studied before the normal spatial vectorcardiogram can be adequately defined. It is also important to realize that we have divided the spatial vectorcardiogram into two types entirely for convenience and that we use them in our analyses for the same reason. Eventually, and as soon as possible, such a division should be discarded, for obviously it will tend to restrict analyses.

Certain characteristics of the configurations and spatial orientations of the spatial vectorcardiogram are presented in the tables and configurations. Unfortunately, the recordings were not satisfactory for a study of the P and T $s\hat{E}$-loops of all subjects. The limited number of records suitable for P and T $s\hat{E}$-loop analyses were only sufficient to define the patterns in general.

One of the major shortcomings in vectorcardiography is failure of the records to present an adequate time scale. The records do not indicate the duration of the P–R interval, Q–T interval, or even the QRS itself. Until this disadvantage is overcome, spatial vectorcardiography cannot replace electrocardiography.

Attempts were made to derive the precordial leads from the superior plane projection of the spatial vectorcardiogram obtained with the use of the equilateral tetrahedron in 63 subjects and from the horizontal projection obtained with the use of the cuboidal reference frame in 25 subjects.[13] Only general configurations were obtained. There was failure in those derivations in important details. For example, R′ deflections, which by accepted criteria would indicate right bundle branch block or defective conduction in the right bundle branch, were obtained in leads V_1 and V_2 in records of normal subjects. Such R′ waves did not exist in the actually recorded V_1 and V_2 leads. Large S waves were derived for V_5 and V_6 when actually recorded V_5 and V_6 did not reveal S waves. Errors in T-wave derivations were also obtained. When such errors are encountered in the derivation of the unipolar precordial leads from the spatial vectorcardiogram, similar errors in the construction of the

spatial vectorcardiogram from the unipolar leads would be expected. One of the most important factors responsible for such errors is difference in electrode positions. The relative nearness, anatomically and electrically, of the precordial leads to the heart is especially important, in addition to the fact that the electrode positions for the precordial leads are different from those employed in recording the spatial vectorcardiogram.

It is not practical to construct the frontal plane projection of the spatial vectorcardiogram, with its detailed configuration, from the standard leads of the electrocardiogram. Significant differences existed between the constructed loops and those recorded by the cathode ray oscilloscope. As would be expected from the preceding paragraphs, the spatial vectorcardiograms constructed from the standard leads and the unipolar precordial leads were even more different from those recorded oscilloscopically. That such difficulties in construction were encountered is not surprising when the differences in the methods of recording are considered. Surely, for more thorough investigation of the spatial vectorcardiogram, the automatic recording by means of the oscillographic method is necessary. Certain general investigations are possible by manual construction, but the tedious nature and possible serious errors due to failure to reveal small but important factors and temporal variations may result in significant erroneous conclusions. Spatial vectorcardiograms constructed manually from the precordial leads with their semidirect electrode positions should be viewed with extreme skepticism and compared cautiously, if at all, with spatial vectorcardiograms recorded automatically from different electrode positions.

Obviously, it is, for the moment, absurd to refer to the "correct" or "absolutely true" complexes of the spatial vectorcardiogram. The configurations and orientations of the recorded spatial vectorcardiogram are determined in part by the method employed in the recording. It is better to refer to the spatial vectorcardiogram as having been recorded with a certain spatial reference frame.

The records used in these studies did not include an adequate time scale, which is a deficiency of the spatial vectorcardiogram as presently recorded. Although it was not possible, by means of the spatial vectorcardiogram, to detect any abnormalities related to certain temporal phenomena which might have existed, electrocardiograms recorded on the same occasion indicated that there were no such disturbances in these subjects.

Unfortunately, the P sÊ-loops were not satisfactory for analysis in every record. This was true to a lesser extent for the T sÊ-loops. Until the methods of recording are improved, vector quantities located near the isoelectric point will usually be obscured by the movement of the cathode ray beam near this point. This movement is produced by noises in the amplifier circuits, skin currents, extrinsic alternating currents, and currents from skeletal muscular contractions. Furthermore, with overexposure during photography, a small halo contributes to the obscuring difficulties. The vector forces of the QRS sÊ-loop near the isoelectric point are also obscured by these artefacts.

The irregularities along the efferent limb of the T sÊ-loop have concerned us for some time. Limited studies suggest that most of them are artefacts due to alternating current interference and to currents from skeletal muscle contractions. These artefacts produce more readily detectable irregularities in the afferent limb than in the efferent limb because the trace is usually moving slowly when the efferent limb is inscribed and rapidly when the afferent one is inscribed. These same artefacts are probably also responsible for some of the irregularities in contour of the P and QRS sÊ-loops. There is a decided need to study and differentiate the alterations in contour of the loops produced by artefacts from those produced by electric events originating in the heart. The cathode ray oscilloscope will record high frequency electric phenomena, cardiac and extracardiac in origin, which are not recorded in the conventional electrocardiogram. It will be necessary to become acquainted with them and to differentiate those which are cardiac from those which are extracardiac.

As indicated by Duchosal,[22] the "electric dipole" of the heart shifts during the cardiac cycle and during respiration, not only because of events related to variations in the order of electric processes within the heart but also because of shifting of the heart within the chest as it beats. The influence of this changing position upon the configuration of the spatial vectorcardiograms and the spatial electrocardiograms has not been thoroughly evaluated. This drifting must influence the accuracy of the electrocardiogram manually constructed from the spatial vectorcardiogram and vice versa.

Summary

The spatial vectorcardiograms of 75 normal young adults, recorded with use of the equilateral tetrahedral reference system, have been studied with the following observations.

1. The normal QRS sÊ-loops studied were of two basic forms, the majority being elliptoid and the remainder having a roughly circular contour.

2. There were wide variations in the orientation of the QRS sÊ-loops about their anteroposterior, transverse, and longitudinal axes.

3. These variations in orientation accounted for the extreme variability in shape and direction of inscription of the plane projections of the QRS sÊ-loop and of the electrocardiographic leads of these subjects.

4. The classification of two varieties of contour of the QRS sÊ-loop, with a wide range of orientation, simplified recognition of normal spatial vectorcardiograms and their differentiation from the abnormal.

5. The factors which probably influence the form and orientation of the spatial vectorcardiogram are listed and discussed.

6. The T sÊ-loops of these subjects also showed only two basic forms (elliptoid and circular) but had wide variations in orientation.

7. The relation of the precordial leads to the spatial vectorcardiogram was studied, and it was concluded that detailed characteristics of the form and magnitude of the precordial leads cannot be inferred from the vectorcardiogram.

8. The advantages of the equilateral tetrahedron as a reference system for spatial vectorcardiography are discussed.

Sumario Español

Los vectorcardiogramas espaciales de 75 sujetos normales han sido estudiados y algunas de las caracteristícas de los trazados se describen. Se encontró que las deflecciones QRS sÊ y T sÊ tienen solamente dos configuraciones espaciales básicas pero con una variedad de orientaciones que producen muchas diferentes proyecciones planares; en parte esto explica la variación tan grande del vectorcardiograma normal. El significado de este y otros hallazgos se discute y ciertos conceptos pertinentes del estudio del vectorcardiograma se presentan.

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The Spatial QRS Loop in Right Ventricular Hypertrophy with Special Reference to the Initial Component

By Noble O. Fowler, Jr., M.D., and Robert A. Helm, M.D.

Spatial vectorcardiograms were recorded from 18 subjects with normal electrocardiograms and from 14 subjects with electrocardiograms indicative of right ventricular hypertrophy. In the latter group there was a significant incidence of deviation of the initial portion of the QRS loop from the normal direction of inscription, suggesting that activation of the interventricular septum often proceeds in an abnormal manner in right ventricular hypertrophy. A statistically significant difference in the direction of rotation of the entire QRS loop in the transverse and sagittal planes was noted in the two groups. The relationship between the direction of inscription of the QRS loop in the transverse plane and the timing of the intrinsicoid deflections of precordial leads is discussed.

IN an earlier paper it was demonstrated that the normal rS* pattern in the electrocardiogram of the right ventricular cavity is sometimes replaced by a QS pattern in right ventricular hypertrophy.[1] This condition was shown to obtain in five of seven cases of right ventricular hypertrophy who had a qR pattern in electrocardiographic V leads from the right precordium.[1, 2] It was believed that further information concerning this problem might be obtained from a study of the spatial QRS loop by means of the vectorcardiograph, paying special attention to the initial portion of the QRS loop.

Material

Eighteen convalescent patients with normal scalar electrocardiograms were studied from the medical wards of the Cincinnati General Hospital. These are listed in table 1. Fourteen patients with right ventricular hypertrophy were studied from the medical wards and the Out-Patient Department of the Cincinnati General Hospital. These subjects and their diagnoses are given in table 2. The criteria of selection of the latter were: (1) the presence of a clinical condition usually associated with right ventricular hypertrophy; (2) the presence of a qR, Rs or rsR′ pattern associated with a QRS complex of normal duration in V leads obtained from the right precordium. Through cardiac venous catheterization, right ventricular or pulmonary artery pressures were available in 7 of the 14 patients. The pulmonary artery pressures in millimeters of mercury were: F.W., 122/38; D.M., 70/26; M.H., 49/22; R.P., 81/32; I.E., 45/21; right ventricular systolic pressures were: R.T., 165; R.M., 170. In six of the seven remaining subjects cardiac x-ray films showed dilated pulmonary arteries. The remaining subject had no x-ray study or catheterization. One subject (A. H.) had a qR pattern in a right precordial V lead associated with a QRS of 0.12 second duration; however his x-ray film indicated definite right ventricular hypertrophy.

Method

The spatial vectorcardiogram was inscribed in its frontal, sagittal, and transverse projections, using the method of Grishman.[3] Three mutually perpendicular leads radiating from a common electrode located at the level of the second lumbar vertebra in the right posterior axillary line are arranged in the form of a rectilinear parallelepiped with approximately equal sides (cube). The frontal projection was viewed from the front of the erect subject, with the right posterior axillary electrode positive for the vertical component and the left posterior axillary electrode positive for the horizontal component. The sagittal projection was viewed from the erect subject's right side, with the right posterior axillary electrode positive for the vertical component and the right anterior axillary electrode positive for the horizontal component. The transverse projection was viewed as if looking from above toward the head of the prone subject, with the right anterior axillary electrode positive for the vertical

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* Following the usual convention, a capital letter indicates a relatively large deflection; a small letter indicates a relatively small deflection.

TABLE 1.—*Normal QRS Spatial Loops*

Subject	Direction Frontal Plane Loop	Direction Sagittal Plane Loop	Direction Transverse Plane Loop	QRS Loop Direction 1st 0.004 sec.	QRS Loop Direction 2nd 0.004 sec.	QRS Loop Direction 3rd 0.004 sec.
1. K.W. (M) (25)	Clockwise	Clockwise	Counter-clockwise	Right anterior superior	Right anterior superior	Right anterior superior
2. L.R. (F) (17)	Clockwise	Clockwise	Counter-clockwise	Right anterior superior	Right anterior superior	Right anterior superior
3. J.J. (M) (42)	Counter-clockwise	Clockwise	Counter-clockwise	Left anterior inferior	Left posterior inferior	Left posterior inferior
4. A.T. (M) (29)	Counter-clockwise	Clockwise	Counter-clockwise	Left anterior inferior	Left anterior inferior	Left anterior inferior
5. K.W. (F) (18)	Counter-clockwise	Clockwise	Counter-clockwise	Right anterior superior	Right anterior inferior	Left anterior inferior
6. T.S. (F) (18)	Counter-clockwise	Clockwise	Counter-clockwise	Right anterior inferior	Right anterior inferior	Right anterior inferior
7. V.McC.* (F) (59)	Counter-clockwise	Clockwise	Counter-clockwise	Right anterior inferior	Right anterior inferior	Left inferior
8. J.W. (F) (36)	Indeterminate	Clockwise	Counter-clockwise	Right anterior	Right anterior inferior	Left anterior inferior
9. M.L. (F) (18)	Indeterminate	Clockwise	Counter-clockwise	Right anterior superior	Right anterior superior	Left anterior inferior
10. H.K. (M) (50)	Indeterminate	Clockwise	Counter-clockwise	Right anterior superior	Right anterior superior	Left anterior inferior
11. H.P. (M) (27)	Clockwise	Clockwise	Counter-clockwise	Right anterior superior	Left anterior inferior	Left anterior inferior
12. E.S. (F) (40)	Clockwise	Clockwise	Counter-clockwise	Right anterior	Left anterior	Left anterior inferior
13. F.C.* (M) (46)	Indeterminate	Clockwise	Counter-clockwise	Anterior inferior	Left anterior inferior	Left inferior
14. S.B. (F) (29)	Clockwise	Clockwise	Counter-clockwise	Right anterior inferior	Right anterior inferior	Superior
15. J.S. (M) (39)	Clockwise	Figure 8	Counter-clockwise	Right anterior superior	Right anterior superior	Left posterior superior
16. E.W. (F) (28)	Counter-clockwise	Clockwise	Counter-clockwise	Right anterior inferior	Right anterior inferior	Right anterior inferior
17. E.B. (M) (28)	Counter-clockwise	Clockwise	Counter-clockwise	Right anterior inferior	Right anterior inferior	Left inferior
18. C.C. (M) (27)	Clockwise	Clockwise	Counter-clockwise	Right anterior superior	Right anterior superior	Left anterior inferior

* Mild hypertension.

TABLE 2.—*Spatial QRS Loops in Right Ventricular Hypertrophy*

Subject	Right Precordial ECG	Direction Frontal Plane Loop	Direction Sagittal Plane Loop	Direction Transverse Plane Loop	QRS Loop Direction 1st 0.004 sec.	QRS Loop Direction 2nd 0.004 sec.	QRS Loop Direction 3rd 0.004 sec.
1. R.T.* (M) (23) Pulmonic stenosis	rsR′ in V_1	Clockwise	Counter-clockwise	Counter-clockwise	Anterior superior	Right superior	Right superior
2. A.H. (M) (39) Prob. high ventricular septal defect	qR in V_1	Counter-clockwise	Clockwise	Clockwise	Right posterior inferior	Posterior inferior	Posterior inferior
3. F.W.* (F) (40) Atrial septal defect	qR in V_1	Clockwise	Counter-clockwise	Clockwise	Left anterior inferior	Left anterior inferior	Left anterior inferior
4. C.C. (F) (15) Prob. atrial septal defect	qR in V_{4R}	Clockwise	Triple 8, major segment clockwise	Clockwise	Right anterior superior	Right anterior superior	Right anterior superior
5. R.M.* (F) (32) Primary pulmonary hypertension	Rs in V_{5R}	Clockwise	Clockwise	Counter-clockwise	Anterior inferior	Left anterior inferior	Left anterior inferior
6. D.M.* (M) (46) Cor pulmonale	rsR′ in V_1	Clockwise	Counter-clockwise	Figure 8, initially clockwise, terminally counter-clockwise	Left posterior inferior	Left anterior inferior	Left anterior inferior, turning right
7. M.H.* (F) (30) Mitral stenosis	R in V_1, V_{4R}	Clockwise	Clockwise	Clockwise	Left anterior inferior	Left anterior inferior	Left anterior inferior
8. A.J. (F) (40) Mitral stenosis	qR in V_1	Clockwise	Counter-clockwise	Clockwise (variable)	Left posterior inferior	Left posterior inferior	Left posterior inferior
9. R.P.* (F) (26) Atrial septal defect	qR in V_{4R}	Clockwise	Counter-clockwise	Clockwise	Left anterior inferior	Left inferior	Left inferior
10. M.S. (M) (47) Mitral stenosis	R in V_1 & V_4R	Clockwise	Counter-clockwise	Clockwise	Left anterior superior	Left anterior superior	Left anterior inferior
11. E.H. (M) (58) Cor pulmonale	qR in V_{4R}	Figure 8 proximally clockwise	Clockwise	Clockwise	Left superior posterior	Left superior posterior	Left inferior
12. I.E.* (F) (25) Mitral stenosis	rsR′ in V_1	Counter-clockwise	Clockwise	Counter-clockwise	Right anterior superior	Right anterior superior	Left anterior inferior
13. M.R. (F) (20) ? Atrial septal defect	R in V_1 rsR′ V_{4R}	Clockwise	Figure 8 counter-clockwise distally	Clockwise	Right anterior	Right anterior inferior	Left anterior superior
14. G.P. (M) (42) Cor pulmonale	qRs in V_{3R} V_{4R}	Clockwise	Counter-clockwise	Clockwise	Left posterior superior	Left posterior inferior	Right anterior inferior

* Cardiac catheterization.

component and the left posterior axillary electrode positive for the horizontal component. Equal standardizations were used for the vertical and horizontal components of each plane.

The spatial QRS loops were inscribed upon a cathode ray oscilloscope, using the Technicon vectorcardiograph. The cathode ray beam was interrupted 250 times per second by means of an electronic switch. The segments of the interrupted beam were pointed in the direction of motion by a square wave generator modified by a capacitor. The frontal, sagittal, and transverse QRS loops were photographed successively upon 35 mm. film and enlarged by projection for detailed study.

Scalar electrocardiograms were recorded in 12 of the 14 cases of right ventricular hypertrophy by means of the Technicon Triagram Electrocardiograph. In the other two and in the normal subjects the Sanborn Visocardiette was used.

RESULTS

These are given in tables 1 and 2 and in figures 1 through 5.

In the normal subjects (table 1), the sagittal plane QRS loop was inscribed in a clockwise direction in all cases with one exception (patient J. S.). The transverse plane QRS loop was inscribed in a counterclockwise direction

in all normal subjects. The inscription of the frontal plane QRS was variable. These findings are similar to those reported by Grishman and Scherlis.[3] The initial QRS loop was directed to the right and anteriorly in 15 of our 18 normal subjects. A typical example is illustrated in figure 1 (C. C.). However, the initial QRS loop in two of the normal subjects, one of which is illustrated in figure 2 (J. J.), was directed to the left and anteriorly. In the remaining normal subject, the initial QRS loop was directed anteriorly without lateral deviation. In none of the 18 normal subjects was the initial QRS loop directed posteriorly.

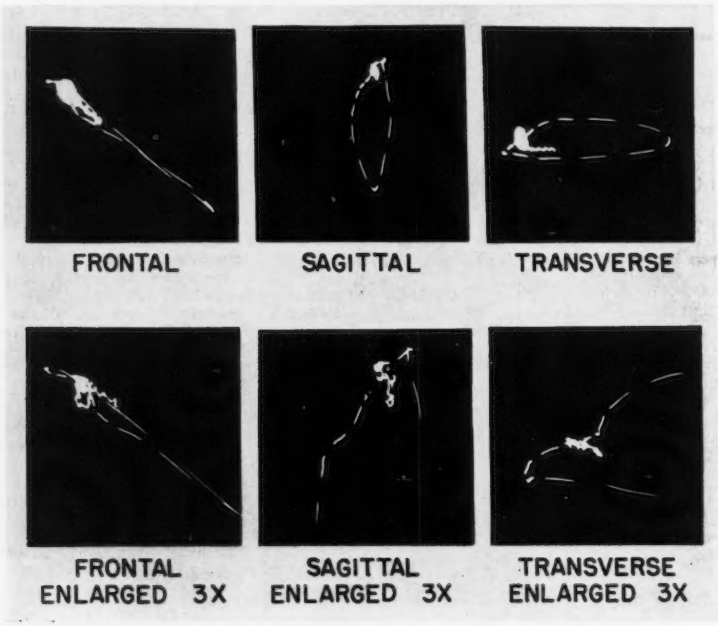

FIG. 1. Spatial vectorcardiogram of a normal 27 year old man showing initial QRS loop direction to the right, superiorly and anteriorly. Note the counterclockwise direction of the transverse plane QRS loop.

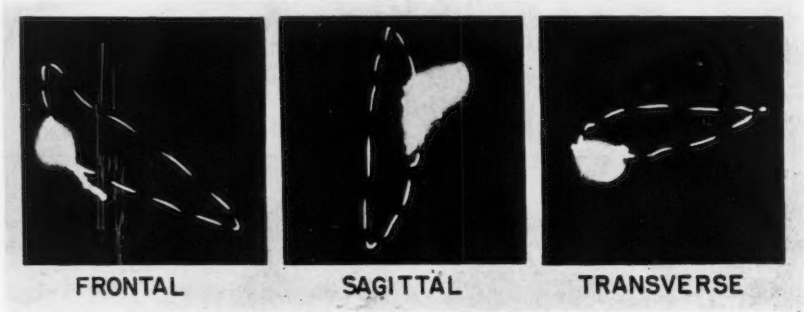

FIG. 2. Spatial vectorcardiogram of a normal 42 year old man showing initial portion of QRS loop directed to the left and inferiorly. Note counterclockwise direction of QRS loop in transverse plane.

In the group with right ventricular hypertrophy, 11 of the 14 demonstrated clockwise

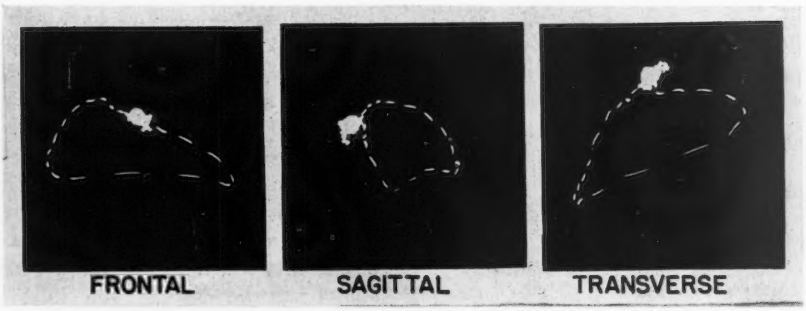

FIG. 3. Spatial vectorcardiogram of a 26 year old woman with auricular septal defect and right ventricular hypertrophy, showing initial direction of QRS loop to the left, anteriorly and inferiorly. Note clockwise direction of transverse plane QRS loop.

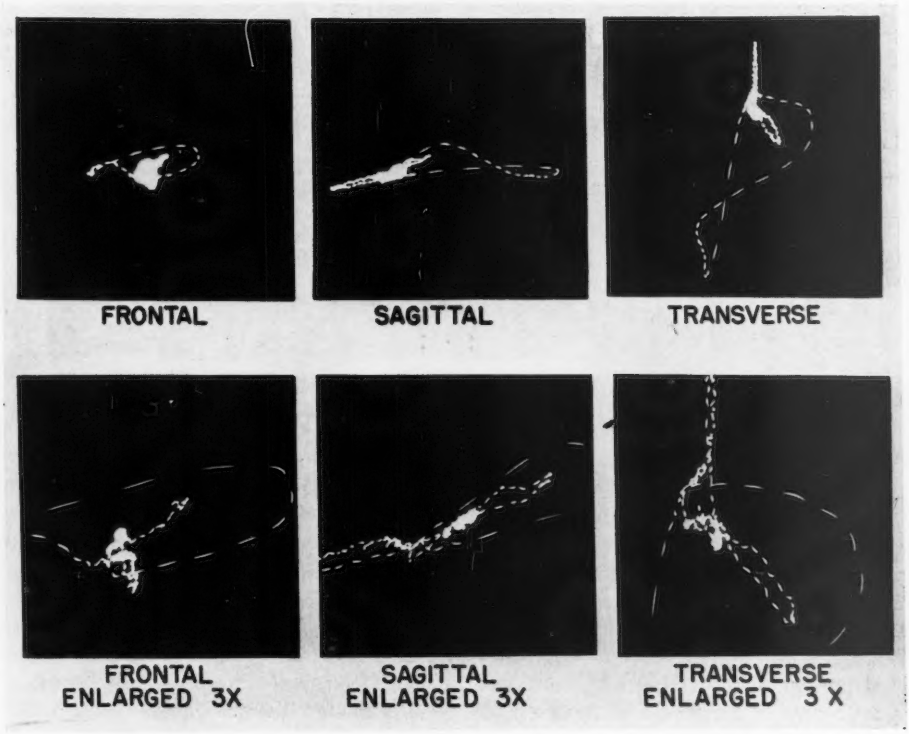

FIG. 4. Spatial vectorcardiogram of a 39 year old man with probable high ventricular septal defect and with right ventricular hypertrophy, showing initial QRS loop directed posteriorly and inferiorly. QRS loop in transverse plane describes a figure of eight with the larger portion directed clockwise.

rotation of the QRS loop in the transverse plane. Examples are illustrated in figures 3 (R. P.), and 4 (A. H.). A counterclockwise transverse plane QRS loop in right ventricular hypertrophy is seen in figure 5 (R. M.). The difference from the normal group in rotation in the transverse plane is significant ($X^2 = 21.53$; $p < 0.001$).

Eight of the 14 cases of right ventricular hypertrophy had counterclockwise rotation

of the QRS loop in the sagittal plane, contrasted with none of 18 in the normal group. The difference is significant statistically (X^2 = 10.08; p = <0.01). Counterclockwise rotation of the sagittal loop in right ventricular hypertrophy is illustrated in figure 3.

Eleven of 13 cases of right ventricular hypertrophy demonstrated clockwise rotation of the QRS loop as seen in the frontal plane, contrasted with 7 of 14 in the normal group. The difference is of borderline significance statistically (p = 0.05).*

from the right precordium have been discussed previously.[1] The finding of initial direction of the spatial QRS loop to the right and anteriorly in the majority of normal persons is consistent with the theory that the left side of the interventricular septum is usually activated earlier or more completely than the right. This initial direction of the QRS loop is to be expected from the anatomic position of the interventricular septum. Our previous study[1] suggested that the interventricular septum was not activated from left to right, in

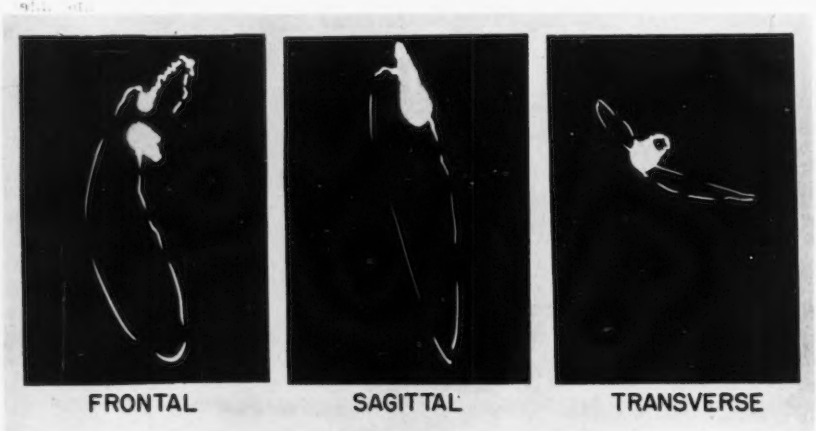

FIG. 5. Spatial vectorcardiogram of R. M., a 33 year old woman with right ventricular hypertrophy due to primary pulmonary hypertension. Initial QRS loop is directed anteriorly and inferiorly, then to the left.

The finding of an initial direction of the QRS loop to the left or posteriorly in 8 of 14 cases of right ventricular hypertrophy as contrasted with 3 of 18 of the normal group indicated a difference of significance (X^2 = 7.619; p <0.01).

Initial QRS loop activation contrary to the expected normal direction in right ventricular hypertrophy is illustrated in figures 3, 4 and 5.

DISCUSSION

The various theories as to the origin of the Q wave in V-lead electrocardiograms recorded

the usual fashion in some cases of right ventricular hypertrophy, thus accounting for the Q wave over the right precordium. If one accepts the concept that the earliest portion of the spatial QRS loop results from activation of the interventricular septum, then the present study would tend to support our previous findings. The abnormal initial direction of the spatial QRS loop in 8 of 14 cases of right ventricular hypertrophy suggests that septal activation is partly or completely reversed in a number of these cases, possibly due to hypertrophy of the right side of the septum. Reversed initial QRS spatial loops were found in seven of eight patients having initial Q waves in right precordial V leads (table 2), suggesting that the initial Q wave is of value in detecting this situation.

* Determined from the direct probability formula[4].

$$p = \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{n!} \qquad \frac{1}{a!b!c!d!}$$

Grishman[3] found abnormal initial direction of the QRS spatial loops in two cases of right ventricular hypertrophy, but considered this an unusual observation. The finding of abnormal direction of the initial portion of the QRS loop in 3 of 18 subjects with normal electrocardiograms suggests that septal activation does not proceed from left to right invariably in the normal heart. Levine's failure to find initial small R waves with multiple exploratory right ventricular cavity leads in 3 of 27 normal subjects tends to support this explanation.[5]

The highly significant difference in the direction of inscription of the transverse plane QRS loops in the normal subjects and those with right ventricular hypertrophy coincides with the findings of Grishman and associates.[3] In the normal group the posterior limb of the transverse plane QRS loop was invariably convex posteriorly. In two of our three cases of right ventricular hypertrophy exhibiting counterclockwise rotation, the loop was narrow and the posterior limb was concave posteriorly (fig. 5). Whether or not such a configuration has a significance analogous to clockwise rotation in this plane will require further study. In the remaining case of counterclockwise rotation, the orientation of the transverse plane QRS loop was bizarre.

Analysis of the transverse plane loop indicates that inscription in a clockwise or counterclockwise direction respectively depends essentially upon whether the potential difference recorded by the sagittal lead is developing positivity or negativity at the time of, or immediately after, the development of the peak of positivity of the potential difference recorded by the horizontal lead. In right ventricular hypertrophy analysis of simultaneously recorded leads over the left precordium (V_5 or V_6) and leads over the right precordium demonstrating prominent R waves (V_{4R}, V_{3R}, or V_1), indicates that the same relationships obtain, the right precordial leads recording initial or increasing positivity at the instant the peak of positivity is attained over the left precordium. It would seem, therefore, that the direction of inscription of the transverse plane vectorcardiographic QRS loop yields information of the type obtained by a study of the time of onset of the so-called intrinsicoid deflections in right and left precordial leads. The latter measurements, however, are difficult and unreliable unless the leads are recorded simultaneously for direct timing of the R peaks, since the onset of QRS is invariably asynchronous in different leads.

Summary and Conclusion

Study of the spatial QRS loop in 18 normal subjects and in 14 cases of right ventricular hypertrophy indicated the following:

1. The initial portion of the spatial QRS loop was inscribed posteriorly or to the left significantly more often in the group with right ventricular hypertrophy. This suggests that activation of the interventricular septum often proceeds in an abnormal manner in right ventricular hypertrophy.

2. The QRS loop was inscribed in a clockwise direction in the transverse plane significantly more often in the subjects with right ventricular hypertrophy.

3. The QRS loop was inscribed significantly more often in a counterclockwise direction in the sagittal plane in the group demonstrating right ventricular hypertrophy.

4. The QRS loop was inscribed in a clockwise direction in the frontal plane more often in the group with right ventricular hypertrophy than in the normal group. The difference is of borderline statistical significance.

Sumario Español

Vectorcardiogramas espaciales fueron registrados en 18 sujetos con electrocardiogramas normales y en 14 sujetos con electrocardiogramas indicativos de hipertrofia ventricular derecha. En el último grupo hubo una incidencia significativa de desviación de la porción inicial de la deflección QRS de la dirección normalmente observada, sugiriendo que la activación del tabique interventricular a menudo procede de manera anormal en hipertrofia ventricular derecha. Una diferencia estatística significativa en la dirección de rotación de todo el complejo QRS en los planos transversales y sagitales se observó en ambos grupos. La relación entre la dirección de inscrip-

ción del complejo QRS en el plano transversal y el tiempo de las deflecciones intrinsecoides de las tomas precordiales se discute.

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The Heparin-Like Action of Treburon in Abolishing Alimentary Lipemia in Normal Individuals

By Robert F. Ackerman, M.D., and D. B. Zilversmit, Ph.D.

The effectiveness of Treburon in clearing alimentary lipemia in young adults has been studied. It is shown that the optical density of plasma at 650 mμ is a satisfactory measure of "physical" lipemia. A significant difference was noted in the extent of alimentary lipemia of young males and females.

In 1943 Hahn[1] observed that heparin would clear lipemic plasma a few minutes after its intravenous administration. However, no clearing action of heparin was apparent when heparin was mixed with plasma in vitro. This observation has been confirmed by several other groups.[2, 3] Apparently heparin clears lipemic plasma by altering the physical state of the blood lipids since their chemical composition is not changed.[4]

Treburon,* a synthetic material, has a heparin-like action in preventing blood clotting.[5-7] Therefore, Treburon might also abolish alimentary lipemia. The following studies were undertaken to investigate the action of Treburon on alimentary lipemia in man.

Methods

Our procedures paralleled those of Block and Barker,[4] except that Treburon was employed instead of heparin. A fasting sample of blood was drawn and 260 cc. of 36 per cent cream was then fed to each individual. A second blood sample was drawn three hours later. From a tuberculin syringe, a measured amount of Treburon was injected intravenously at that time and 15 minutes later the third blood sample was drawn. All blood samples were oxalated and centrifuged to separate the plasma. Timing was arranged so that the turbidity of all samples was measured one hour after the last blood sample had been drawn. The turbidity of the plasma samples was determined with a Beckman Spectrophotometer by measuring the optical density at 650 mμ against a distilled water blank.

In several experiments, chylomicron counts were made on the same plasma samples employed for the turbidity measurements. Lipemic samples were diluted 1:10 or 1:20 with 20 per cent urea before a chylomicron count was made. In confirmation of the work of Marder and associates[8] we found that urea is a more satisfactory diluent than water or saline. Optical densities, which were measured on the diluted and original samples showed a precise proportionality to the extent of dilution, even over a concentration range of 1:100.

In some of the experiments, Treburon was administered sublingually in order to determine whether this material would be active when administered by this route. The Treburon tablets required 15 to 30 minutes to dissolve, consequently, the post-Treburon specimen was drawn approximately 30 minutes after the pre-Treburon blood sample.

Results

Table 1 presents our findings when varying amounts of Treburon were administered to 16 normal, healthy females and 16 normal, healthy male subjects aged 18 to 29 years. The lipemia clearing was calculated as the percentage difference between the turbidity of lipemic and cleared samples. Block and Barker[4] subtracted the optical density of the fasting sample from the other two before they calculated the percentage clearing. We did not use the fasting sample as a blank, however, because several of the fasting samples of the male subjects showed an appreciable optical density due to postabsorptive lipemia. Consequently, the

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* Treburon is the sodium salt of sulfated polygalacturonic acid methyl ester methyl glycoside developed by Hoffmann-La Roche. It was kindly furnished to us through the efforts of Dr. M. J. Schiffrin in 2 cc. ampules containing 50 mg. Treburon per milliliter.

cleared samples sometimes showed lower optical densities than the fasting samples, a situation which would imply more than 100 per cent clearing action of the drug.

Treburon administered intravenously to young males and females in doses of 15 mg. or above showed a consistent lipemia clearing action. Below this dosage the drug showed a clearing effect in a smaller proportion of the individuals. Experiments carried out on 15 older hospitalized female patients showed entirely similar results. In 13 of these patients, doses of Treburon ranging from 15 to 150 mg. produced more than 30 per cent clearing. In two additional patients, saline was injected instead of Treburon. In both patients the degree of lipemia of the third sample was greater than that of the second one.

Treburon was administered sublingually in 500 or 1000 mg. quantities to seven hospitalized female patients. In four patients the lipemia increased, while three showed only 15 to 20 per cent clearing. It is thus evident that Treburon administered by this route has little or no activity in clearing lipemia.

In table 2 the optical densities and chylomicron counts of the fasting, lipemic, and cleared plasma samples of nine subjects are compared. In order to show the close agreement obtained by these two methods of measurement, the values are expressed in arbitrary units in a manner such that the lipemic samples show optical densities and chylomicron counts of 100.

TABLE 1.—*The Lipemia Clearing Action of Treburon in Normal Males and Females*

Males	Treb. mg.	Optical Density‡			Clearing %*		Females	Treb. mg.	Optical Density‡			Clearing %*	
		Fasting	Lipemic	Cleared					Fasting	Lipemic	Cleared		
D. L.	25	.091	.626	.137	78	Av. 70	B. S.	15	.067	.596	.259	57	Av. 40
J. T.	25	.096	1.321	.676	49		J. S.	15	.075	.538	.286	47	
C. Y.	25	.107	.853	.190	78		M. W.	15	.074	.252	.213	15	
T. N.	25	.036	.731	.187	74		M. L.	12	.072	.407	.245	40	
W. S.	15	.131	.498	.057	89	Av. 79	A. W.	10	.104	.570	.208	63	Av. 54
J. S.	15	.311	.700	.249	64		A. S.	10	.115	.351	.175	50	
J. T.	15	.224	1.038	—			J. D.	10	.153	.822	.416	49	
A. V.	15	.072	.469	.074	84		M. G.	10	.061	.234	.272	−16†	
R. K.	10	.432	.559	.362	35	Av. 29	G. A.	5	.080	.396	.114	71	Av. 57
H. M.	10	.065	1.238	.950	23		M. G.	5	.077	.312	.124	60	
L. B.	10	.162	.624	.512	18		M. S.	5	.073	.125	.072	42	
H. C.	10	.092	1.500	.906	40		M. N.	5	.208	.270	.118	56	
J. A.	5	.368	1.651	1.447	12	Av. 39	J. F.	3	.082	.317	.202	36	Av. 32
J. F.	5	.054	.224	.084	62		M. S.	3	.139	.574	.301	47	
J. R.	5	.064	.581	.268	54		C. C.	3	.169	.512	—		
D. H.	5	.076	1.150	.842	27		G. E.	0	.072	.289	.251	13	

* % Clearing = $(100 - \frac{\text{OD cleared plasma}}{\text{OD lipemic plasma}} \times 100)$.

† Not included in average.

‡ Readings in optical density units taken directly from the spectrophotometer scale.

In nearly all instances the agreement is remarkably close. Only in the cleared sample of the second subject is there a disagreement between the results. This deviation can be ascribed to the presence of hemolysis which contributed to the optical density of the sample.

DISCUSSION

Inspection of table 1 reveals that the results obtained with Treburon are very similar to those reported by others using heparin. Whether or not the lipemia clearing activities of Treburon and heparin exist in the same

ratio as their effectiveness as anticoagulants cannot be stated with certainty at this time.

Our results indicate that young males develop a significantly greater degree of lipemia after ingestion of the test meal than do young females.* Such a difference was also noted by Block and Barker,[4] but not by Schwartz and co-workers.[9] If this tendency toward a lesser degree of alimentary lipemia in women can be confirmed, one might speculate whether this observation could explain the lower incidence of atherosclerosis in women before the menopause. The close parallelism between chylomicron counts and optical densities of fasting, lipemic and cleared plasma makes the latter measurement the method of choice for the quantitation of "physical" lipemias. Pigmentation of the plasma will interfere with the measurement of lipemia by light transmission, but the simplicity and time saving aspects of the method as compared with the counting of chylomicrons are so great that an occasional error due to severe hemolysis is no great disadvantage. To avoid this possible error, Marder and co-workers[8] have recommended the use of the nephelometer for the measurement of lipemia. Their data indicate, however, that the chylomicron counts and nephelometer readings are only related in a semiquantitative way. It is possible that nephelometer readings will give a useful measure of opalescence, but as a substitute for chylomicron counts the measurement of optical density appears to be the method of choice.

TABLE 2.—*Comparison between Optical Densities and Chylomicron Counts*

Name		Treburon	Fasting	Lipemic	Cleared
		mg.			
J. F.	O.D.*	5	24	100	38
	C.C.*		25	100	39
H. M.	O.D.	10	5	100	76†
	C.C.		5	100	29
J. R.	O.D.	5	11	100	46
	C.C.		10	100	39
M. G.	O.D.	10	26	100	116
	C.C.		26	100	118
B. S.	O.D.	15	11	100	43
	C.C.		12	100	40
M. L.	O.D.	12	18	100	60
	C.C.		17	100	56
M. G.	O.D.	5	25	100	40
	C.C.		25	100	39
M. S.	O.D.	5	58	100	58
	C.C.		59	100	56
G. E.	O.D.	0	25	100	87
	C.C.		24	100	82

* Optical density and chylomicron count are expressed as percentages; the peak of lipemia is taken as 100 per cent in each instance.

† Considerable hemolysis was present in this sample.

* Fisher's t value was 4.11 which gives a p value of .001.

SUMMARY

1. Following the oral administration of a measured amount of cream, the intravenous injection of Treburon clears lipemic plasma. The smallest amount of Treburon with consistent action in this respect lies between 15 and 25 mg.

2. The sublingual administration of Treburon produces no definite clearing of lipemic plasma.

3. Chylomicron counts and plasma turbidities, as determined by optical densities, are proportional. Therefore, the determination of the plasma turbidity appears to be the simplest substitute for chylomicron counts.

4. After ingestion of cream, young women develop less lipemia than young men.

ACKNOWLEDGMENTS

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SUMARIO ESPAÑOL

La efectividad del Treburon en la prevención de lipemia alimenticia en adultos jóvenes ha sido estudiada. Se demuestra que la densidad óptica del plasma a 650 mμ es una medida satisfactoria de lipemia física. Una diferencia

significativa se notó en el grado de lipemia alimenticia entre el adulto joven varón y la hembra.

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Ventricular Arrhythmia and Stokes-Adams Syndrome

Report of a Case

By Donald A. Dupler, M.D.

An unusual case of ventricular arrhythmia is reported with electrocardiograms showing complete attacks of ventricular tachycardia, ventricular flutter and ventricular fibrillation. The etiology is unknown. Large doses of quinidine, to the point of toxicity, seemed to halt the arrhythmia but did not prevent its recurrence. Ephedrine was given with resulting immediate improvement and no recurrence of the arrhythmia. It is suggested that ephedrine may be of value in treating Stokes-Adams attacks due to ventricular arrhythmia in which there is no heart block but an underlying bradycardia.

In recent years it has been pointed out that the classic Stokes-Adams syndrome of unconsciousness is not produced solely by periods of ventricular asystole occurring in patients with complete heart block;[1, 2, 3] recurrent attacks of loss of consciousness may be due not only to ventricular standstill, but also to ventricular tachycardia, ventricular fibrillation, or all three disturbances occurring in varying sequences. There are few reports of recurrent syncope from ventricular fibrillation without heart block.[4, 5, 6] The number of these in the literature is still very few, but it is apparent that heart block is not necessarily present in these cases and the widest concept of the syndrome should be syncope due to any ventricular arrhythmia.

The following case of a ventricular arrhythmia is reported because of several unusual features. The patient was observed during numerous spontaneous attacks of ventricular tachycardia and fibrillation with accompanying attacks of syncope. The etiology of the arrhythmia and the nature of the underlying heart disease, if any, are obscure. Electrocardiograms taken between attacks show a long Q-T interval, the cause of which is unexplained. Large doses of quinidine to the point of toxicity seemed to halt the arrhythmia, but did not prevent its recurrence. The myocardium degenerated and a fatal outcome seemed inevitable until ephedrine was administered by mouth with resulting or coincident change to normal sinus rhythm and no recurrence of the arrhythmia.

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Case Report

A white woman, age 53, was admitted to The Graduate Hospital on Dec. 1, 1949, with a history of two attacks of syncope and palpitation in the preceding 36 hours. She had been in good health with no history of cardiovascular symptoms until 9:30 a.m. the preceding day when she suddenly noticed a palpitation in her chest and felt faint and apparently lost consciousness for a few moments. When seen within an hour she felt weak, but appeared entirely normal. Physical examination was negative. The heart rate was 76 per minute and the rhythm was regular. Blood pressure was 120/80. She was started on quinidine sulfate, 180 mg. every four hours.

About 11 a.m. the next day she had another attack after which she was admitted to the hospital. A third attack at 7 p.m. was witnessed by the hospital staff and had the following features: She complained briefly of palpitation in chest, suddenly lost consciousness and developed stertorous breathing, followed in a short time by apnea. She became pale; soon a dusky cyanosis developed. With a restoration of normal rhythm there was a rapid return to a normal state. During the seizure the apical beat was chaotic, very rapid, or absent; the peripheral pulse was absent. This was the pattern of subsequent attacks which lasted from a few seconds to one or two minutes. In the ensuing 10 days these episodes recurred with varying frequency.

Past history was negative for any significant illness. Physical examination revealed a well-developed, well-nourished woman whose complete examination was negative. The heart was normal in

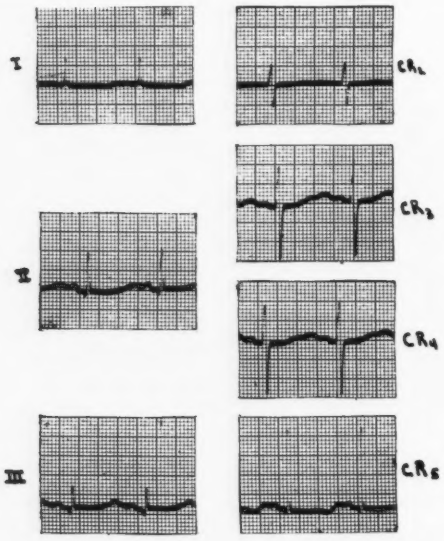

FIG. 1. Electrocardiogram taken on admission, Dec. 1, 1949 at 4 p.m. showing normal sinus rhythm. Notice the long Q-T interval.

size, rhythm was regular except during the attacks described above. Blood pressure was 140/80 on admission and usually 120/80. Laboratory studies were normal. These included: urinalysis, complete blood count, sedimentation rate, blood sugar, blood urea nitrogen, carbon dioxide combining power, serum calcium, phosphorus, potassium, total proteins and chlorides. Cold agglutinins were negative on December 12. Agglutination for brucellosis was positive in dilution at 1:320 on December 16; this dropped to 1:160 on January 3 and 1:80 on January 9. Agglutinations for typhoid, paratyphoid, proteus OX2 and OX19 were negative. Subsequent serologic studies were done by the virus diagnostic research laboratory at the Children's Hospital in Philadelphia and were negative for influenza A, influenza B, Q fever, and the psittacosis-lymphogranuloma venerium group. Cold agglutination test was negative in dilutions of 1:40 or higher in that laboratory also.

The electrocardiogram taken on admission at 4 p.m. December 1 is shown in figure 1. The striking feature is the long Q-T interval. Figure 2 shows the first attack which we were able to record graphically.

As soon as the type of arrhythmia was determined to be ventricular tachycardia she was given quinidine gluconate,[8] 0.6 Gm. intramuscularly every two hours.

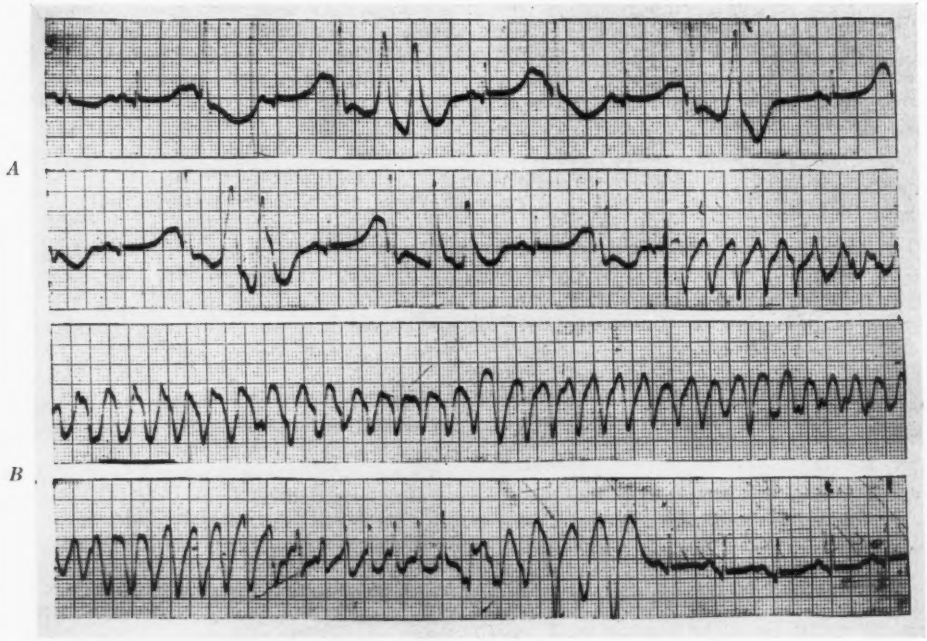

FIG. 2. Tracing taken at 7:45 p.m. Dec. 1, 1949 showing attack before quinidine was started. (*A*) Note the normal sinus rhythm, the long Q-T interval, and the frequent premature beats which occur just after the T waves at the so-called "supernormal" time in the cycle. (*B*) Ventricular and nodal tachycardia, and the termination of the attack.

Within 15 minutes after quinidine was started she had two short attacks, following which there were no seizures that day. Sedation was given for restlessness and apprehension.

The type of arrhythmia appeared to be ventricular tachycardia; later attacks showed ventricular fibrillation and combinations of the two. Figure 3 is an example of a complete attack which was recorded graphically. The cause of the whole picture was obscure.

Large doses of quinidine were given intramuscularly to prevent and to treat attacks. Every one to three hours she received 0.6 Gm. of quinidine gluconate intramuscularly or quinidine sulfate by mouth in addition. During severe attacks she received quinidine intravenously in doses of 60 to 180 mg. to terminate the alarming immediate episode. Attempts to decrease the dose of quinidine were met with recurrence of the attacks each time. A total of 64.4 Gm. of quinidine were given in the 10-day period. On this dosage she developed a blood pressure of 80/60, urinary retention due to loss of bladder tone, deafness, tinnitus, abdominal distention, mental confusion and a diffuse erythematous skin rash.

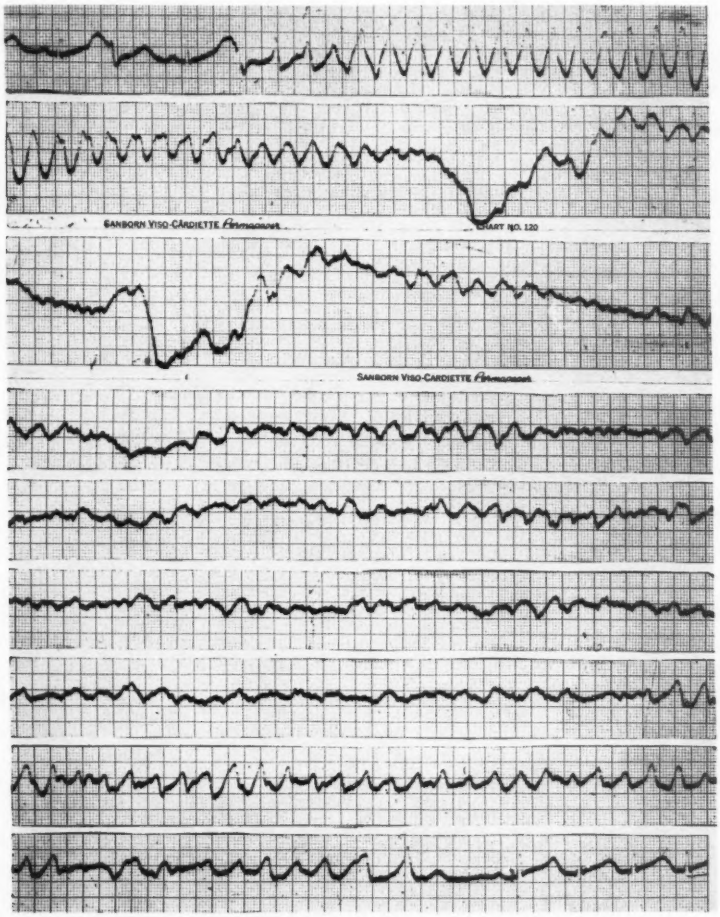

FIG. 3. Tracing taken at 7:30 a.m. on Dec. 5, 1949 showing a complete attack. Note the rhythm just before the onset, ventricular tachycardia, ventricular fibrillation, ventricular flutter-fibrillation, and the ending of the attack.

On December 10, in spite of the toxic doses of quinidine, she continued to have short attacks. As the day progressed she gradually became worse. A heavy substernal distress developed, dyspnea became more evident, and she became slightly cyanotic. Bilateral dullness developed over the lower

lobes of both lungs; the heart was larger by percussion. An x-ray film of the chest, made at the bedside, showed enlargement of the heart and a bilateral diffuse density of the lung fields which "could be due to either pulmonary congestion from heart failure or a diffuse pneumonitis."

It appeared obvious that a fatal outcome was imminent. At 10 p.m. the following changes in therapy were made: Quinidine was stopped. Ephedrine sulfate, 23 mg. by mouth every three hours, was started. Aureomycin in full therapeutic doses was given in view of a possible developing pneumonitis and also in view of the possibility she may have had a myocarditis of unknown or virus etiology which might be benefited by this antibiotic. A mercurial diuretic was given intramuscularly in view of the pulmonary congestion, but no diuresis resulted.

After these changes in medication there were no more attacks. During the next day she gradually improved. An electrocardiogram showed a normal sinus rhythm with an occasional ventricular premature beat. The heart rate increased to about 90 per minute. The dose of ephedrine was decreased to 23 mg. every four hours. The second day she had no complaints. Pulmonary symptoms and signs disappeared. Bladder tone improved and she voided normally. All signs of quinidine toxicity disappeared. A low grade temperature of 99 to 100 which had developed in the preceding three days returned to normal. Her mental confusion cleared completely.

The subsequent course was uneventful except for a few minor details. The multiple quinidine injections had proved very irritating. She developed several sterile abscesses and sloughs deep in the buttocks which took about three months to heal. Occasional premature contractions persisted throughout her hospital course. She was very apprehensive of these and was very slow to resume much physical activity.

Aureomycin was stopped after 17 days. Ephedrine was decreased to 23 mg. every six, then eight hours, and stopped after 30 days. She was discharged from the hospital 61 days after admission. After several months of very limited activity due to her fear of palpitation, she gradually resumed normal life, and to date has been following a routine life of mild exertion. Six months after her discharge from the hospital an electrocardiogram showed no abnormality except low voltage of the T waves in all leads; the Q-T interval was normal. Physical examination revealed no cardiac abnormalities. She is still very heart conscious and states there is an occasional palpitation, about two to five times a day. No cardiac medication is being taken.

Discussion

A myocarditis of unknown etiology could presumably have caused the disturbances which were present. Conceivably this condition could have produced the striking and unexplained lengthening of the Q-T intervals, a finding which Gittleman and co-workers[7] found in 51 to 89.3 per cent (depending upon the formula used) of 51 cases of proved acute myocarditis. Though we cannot entirely dismiss the possibility, we strongly doubt the existence of acute myocarditis since there was nothing that went with an infectious condition until quinidine had produced severe toxic effects and severe heart failure had developed. The disappearance of the low grade temperature (99 to 100 F.) which then developed as well as all other unfavorable signs and symptoms with the ending of the disappearances of rhythm seemed to be more rapid than would have been likely had an active myocarditis been present. No electrolyte disturbance could be found. We, therefore, could not demonstrate definite evidence of organic heart disease.

The cause of the Q-T interval prolongation is unknown in this case. Bellet[9] in a recent communication, to be published, analyzing 168 cases associated with Q-T prolongation, lists 26 causes. It is evident that the prolonged Q-T interval was of no help in determining the etiology.

The type of arrhythmia during an attack consisted of runs of ventricular tachycardia, a prefibrillary or flutter-type of ventricular tachycardia, and ventricular fibrillation. At no time did she have ventricular asystole. The syncopal attacks during arrhythmia were indistinguishable from those one sees in syncope due to heart block. Therefore, we would include this case in the group of Stokes-Adams seizures due to ventricular arrhythmias other than asystole in complete heart block. We would emphasize, with others, that Stokes-Adams seizures occur in patients with ventricular arrhythmias other than heart block and ventricular asystole.

Quinidine has long been the drug of choice in treating paroxysmal ventricular tachycardia.[10, 11, 12] Recently, procaine amide (Pronestyl) has been used quite successfully and will probably supplant quinidine as the most effective drug.[13]

The treatment of paroxysmal ventricular

fibrillation is much less definite. There is a difference of opinion concerning the value of quinidine.[14–19]

In this case, large doses of quinidine at first seemed to prevent attacks, and when the dose was decreased the arrhythmia recurred. Increasingly large doses to the point of intolerable toxicity did not prevent recurrent attacks. We have found no report in the literature of such a ventricular arrhythmia without heart block which was treated with such large doses of quinidine.

Intravenous morphine and intravenous procaine were of no value in this patient. Procaine amide was not available; its value would have been of great interest.

Ephedrine sulfate was decided upon with the hope of increasing the normal heart rate and thereby increasing the total duration of the refractory state of the ventricular muscle. The basic rhythm between attacks was a normal sinus bradycardia with premature contractions of ventricular or nodal origin. This suggested a vulnerable state of the conduction system and ventricular muscle which predisposed to the arrhythmia. This is in accord with the suggestion of Sprague and Davis[17] that the development of a generalized refractory state of the ventricular muscle following contraction is responsible for the prevention of re-entrant beats and finally fibrillation.

It has been shown by Wiggers[20] that the period of late systole is a vulnerable period and, in order to initiate fibrillation experimentally, an electric or noxious influence with a "fibrillary threshold" must be applied during that period in late systole at which time the muscle has passed out of the refractory phase.

The above two considerations are illustrated by our patient in the rhythm just before the attack started. Note the premature beats came after the T wave which terminated the long Q-T interval. This is the supernormal period mentioned by Nahum and Hoff[21] and the vulnerable period discussed by Wiggers.

The use of ephedrine was questioned considerably for fear it might precipitate attacks in a heart known to be subject to ventricular arrhythmia. It has generally been considered to be contraindicated in patients with ventricular arrhythmias.

The other change in treatment at the turning point in this patient's condition was the administration of Aureomycin. This conceivably could have had a role in the patient's improvement if she had had a myocarditis due to an Aureomycin-sensitive organism. We have no basis for such a presumption and we cannot suggest that the drug influenced the cause of the arrhythmia. On the other hand, we cannot be sure it was not of some benefit.

It would seem from our experience in this case and that of others[2, 4] that ephedrine is of value in treating certain ventricular arrhythmias causing Stokes-Adams attacks. It is suggested that it is of value in those cases in which the ventricular rate is slow and the general refractory state of the ventricular muscle is decreased. This would include the cases of heart block with ventricular standstill and arrhythmias, and those with slow sinus rhythm with transient attacks of ventricular tachycardia, fibrillation or a combination of these. The rationale for the use of ephedrine is to increase the refractory state of the conduction system and ventricular muscle by increasing the heart rate and thereby prevent the arrhythmia.

The formerly held theoretic objection to this drug in patients subject to transient ventricular arrhythmia apparently is not borne out by clinical experience in this and other patients with slow ventricular rates.

Summary

1. A case of Stokes-Adams syndrome has been presented which demonstrates graphically that attacks were due to ventricular tachycardia, ventricular flutter (or prefibrillary tachycardia), and ventricular fibrillation, without heart block or asystole.

2. The underlying etiology is unknown. An abnormally long Q-T interval was present and is unexplained.

3. Large doses of quinidine to the point of intolerable toxicity failed to prevent recurrences. Ephedrine sulfate was given with resulting immediate improvement and no recurrence of the arrhythmia.

4. It is suggested that ephedrine is of value in treating Stokes-Adams attacks due to ventricular fibrillation and impure ventricular tachycardia in which there is a basic slow rate, as well as those due to heart block and asystole. Apparently the drug acts by speeding the rate thus increasing the refractory state of the conduction system and ventricular muscle.

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The author wishes to express his appreciation for the help given by Samuel Bellet, M.D., in the management of this case.

SUMARIO ESPAÑOL

Un caso singular de arritmia ventricular se informa con electrocardiogramas mostrando ataques completos de taquicardia ventricular, undulación ventricular y fibrilación ventricular. La etiología se desconoce. Dosis altas de quinidina, hasta el punto de toxicidad aparentaron arrestar la arritmia pero no evitar su reaparición. Administración de efedrina resultó en inmediata mejoría y sin reaparición de la arritmia. Se sugiere que la efedrina puede ser de valor en la tratamiento de ataques Stokes-Adams debidos a arritmias ventriculares en que no hay bloque cardíaco pero si una bradicardia subyacente.

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CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

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The Nature of Auricular Fibrillation and Flutter: A Symposium

PARTICIPANTS: HANS HECHT, M.D., LOUIS N. KATZ, M.D., ALFRED PICK, M.D., MYRON PRINZMETAL, M.D. AND ARTURO ROSENBLUETH, M.D.

Introduction

By HERRMAN L. BLUMGART, M.D.

THE IDEA of this symposium arose during an informal discussion at a meeting of the Editorial Board of CIRCULATION. Much important evidence recently brought forward by the proponents of various theories of the auricular arrhythmias has been difficult to assess by those not intimately engaged in this field. It is believed that the present symposium by leading authorities clarifies some of the issues involved in the current debate. The admirable skill and lucidity with which the evidence for different concepts has been marshalled and ably summarized will, it is hoped, be of value in the clinical evaluation and further research of these arrhythmias.

The symposium will take the form of concise answers to four questions of fundamental importance by the participants. Each contributor will then elaborate upon his answers in a brief discussion.

QUESTIONS AND ANSWERS

Question 1. Has it been proved that auricular flutter and auricular fibrillation represent the same fundamental mechanism?

Hans H. Hecht, M.D. The Symposium implies that no agreement has been reached on the mechanism underlying the two disorders; consequently the question cannot be answered with factual assurance. There is much circumstantial evidence, accepted by everyone, that the two conditions are only quantitatively different and that whatever mechanism may be responsible, it forms the matrix for both. Experimentally, auricular fibrillation and auricular flutter can be induced by the same procedures and the identical clinical situation may be found with either, though flutter is less common and less easily elicited than fibrillation, it being apparently the less stable disorder of the two. Vagal stimulation by (a) shortening the refractory period and (b) increasing impulse transmission converts flutter to fibrillation. Quinidine and like substances by exerting the opposite effect, convert fibrillation to flutter. Intermediate forms or spontaneous changes from one to the other within seconds are often seen, particularly if suitable precordial or esophageal electrocardiographic explorations are employed, and an imperceptible transition can regularly be noted during digitalis or quinidine medication. Conversion of flutter to paroxysmal auricular tachycardia (usually with some degree of A-V block) is frequently possible, and, again, intermediate forms are often obtained during quinidine treatment. In man, this is less readily accomplished than the conversion of flutter to fibrillation, but the kinship between these two auricular disorders seems fairly obvious, at least in instances where these transitions can be observed.

Louis N. Katz, M.D., and Alfred Pick, M.D. The four questions which Dr. Herrman L. Blumgart has asked us to answer as a part of

the symposium on the nature of auricular flutter and fibrillation serve as the background of the personal opinion expressed by us in our formal presentation to this symposium, and our answer cannot be over-simplified. The reader, therefore, must read our personal opinion to see how we would have answered these four questions. However, if we must summarize our viewpoints, our answer to the first question would be as follows:

It has *not* been proved that the fundamental mechanism of auricular flutter and auricular fibrillation represents the same fundamental process, but the evidence for this is highly suggestive.

Myron Prinzmetal, M.D. Direct electrocardiographic and cinematographic evidence obtained from numerous experimental animals has established that both auricular flutter and auricular fibrillation occur when an ectopic focus on the auricles discharges at rapid rates. Moreover, spontaneous or drug-induced conversions between the two arrhythmias are commonly seen clinically as well as experimentally. These observations indicate that auricular flutter and auricular fibrillation represent the same fundamental disturbance, namely, the rapid discharge of impulses from an ectopic focus, but differ primarily in the rate of auricular activity. However, the mechanical and electrical activity observed in the auricles during flutter and fibrillation is radically different, in some instances presumably because the auricular musculature is unable to maintain organized conduction when the auricular rate exceeds the fibrillation threshold.

Arturo Rosenblueth, M.D. No, but it is very likely that they have the same mechanism.

Question 2. Has the mechanism of auricular flutter and auricular fibrillation been established in the animal?

Hans H. Hecht, M.D. The answer here is no. A circus excitation and circus contraction have been unequivocally demonstrated in lower animals under appropriate conditions, as a characteristic pattern of response of cardiac tissue of certain mass and form. In dogs, a repetitive ectopic focus or an area subjected to continuous stimulation has given rise to mechanical and electrical records that at least closely resemble the spontaneous auricular flutter and auricular fibrillation in man. Older experiments (Garrey) have demonstrated that isolating the focus from the remainder of auricular tissue did not influence or interrupt the irregularity, and this has been used in support of the circus excitation concept. Newer observations (Scherf, Prinzmetal), using a similar technic but different stimuli, have shown that the irregularity *is* interrupted if the focus is severed from the remainder of the auricles, and this is claimed as evidence in favor of a continuously firing single focus. Rosenblueth has recently published a technic of inducing and maintaining a flutter-like disorder in dogs that indirectly supports the concept of circus contractions. His technic has been employed in various laboratories and his observations have been repeatedly confirmed.

Louis N. Katz, M.D., and Alfred Pick, M.D. No. The mechanism of auricular flutter and auricular fibrillation has not been established, but the possibilities in the animal have been narrowed, and there is reason to believe that auricular flutter may include the primary and secondary types of mechanism as outlined in our brief paper which follows.

Myron Prinzmetal, M.D. Auricular flutter produced by local application of aconitine or as an after-effect of electrical stimulation has been demonstrated to consist of rhythmic impulses arising at rapid rates from an ectopic focus and traveling outward in all available directions simultaneously. Auricular fibrillation initiated by similar methods consists of heterorhythmic waves of variable strength, frequency, and velocity occurring simultaneously and superimposed on one another. It should be pointed out that certain workers experienced in the use of Rosenblueth's crush method for producing arrhythmias believe that flutter initiated by this technic involves a circus movement.

Arturo Rosenblueth, M.D. Yes. The mechanism is circus-movement.

Question 3. Has the mechanism of auricular flutter and auricular fibrillation been established in man?

Hans H. Hecht, M.D. The answer again is no. No conclusive observations have been presented to date in support of one or the other of the theories in spite of almost four decades of heated assertions.

Louis N. Katz, M.D., and Alfred Pick, M.D. No. The mechanism of auricular flutter and fibrillation has not been established in man, but the analogy to the animal suggests the same conclusion we have expressed in our answer to question 2.

Myron Prinzmetal, M.D. By means of esophageal and limb-lead electrocardiography as well as high-speed cinematography, auricular flutter and auricular fibrillation in man have been shown to be essentially similar in mechanism to the experimental forms of these arrhythmias produced in dogs by chemical or electrical stimulation.

Arturo Rosenblueth, M.D. No.

Question 4. In the light of present knowledge, which mechanism do you believe to be responsible for auricular flutter and/or auricular fibrillation in man?

Hans H. Hecht, M.D. The apparent similarity of human records of the auricular dysrhythmias under discussion to those experimentally induced does not constitute incontestable proof that they are identical. Even if this were assumed, the differences presently existing in interpreting the basic nature of the disorder as seen in animals only multiply when attempts are made to apply the observations to the clinical disorder in man. The facts that high intraluminal pressures, anoxia, vagal stimulation and other influences induce the irregularities or that a certain spread of auricular excitation may be observed grossly does not favor one concept over the other; changes in the refractory period may predictably influence the characteristics of the disorders irrespective of their presumed mechanism. No common ground can be found which would reconcile fully the views supported by various investigators, nor does it seem possible to disregard one set of experiments in favor of another. It is possible that multiple mechanisms either singly or together may cause the admittedly heterogenous experimental and clinical picture of auricular flutter and auricular fibrillation. In fact, the analysis and scrutiny of known observations makes it likely that this is so. Large circular paths as well as small areas responding in chain-like fashion with continuous re-entry of impulses either with or without persistent ectopic stimulus, or a stimulus without re-entry phenomena could, under appropriate circumstances, disrupt the orderly manner of auricular excitation and result in extrasystolic disorders, paroxysmal tachycardia, auricular flutter and auricular fibrillation.

Louis N. Katz, M.D., and Alfred Pick, M.D. As regards the question of choosing a mechanism to account for flutter and/or fibrillation, this cannot be summarized in a few words. The answer must be sought in our complete presentation, which follows. Any attempt to abbreviate carries with it the hazard of being consciously or unconsciously misinterpreted by vehement protagonists of contrary views.

Myron Prinzmetal, M.D. With the development of new technics of cardiac surgery, it has become possible to study the spontaneous arrhythmias in man by direct methods such as high-speed cinematography and direct lead electrocardiography. These methods have already yielded convincing evidence that the clinical forms of auricular flutter and auricular fibrillation, like their experimentally produced counterparts, do not involve a circus movement. In flutter, the excitation wave travels away from the focus through both auricles simultaneously; in fibrillation, the auricular musculature exhibits heterorhythmic activity different from that observed in any other auricular rhythm.

Arturo Rosenblueth, M.D. I believe that both auricular flutter and auricular fibrillation in man are due to circus movement of impulses around appropriate obstacles.

The Mechanism of Auricular Fibrillation and Flutter

By HANS H. HECHT, M.D.

THE DIAGNOSIS of auricular fibrillation at the bedside is based on detecting the complete irregularity of the heart beat: the "pulsus irregularis, inequalis, deficiens and intermittens," apparently first described by Bouilland in 1836.[1] The diagnosis is *indirect* and therefore occasionally fallacious since (a) a "delirium cordis" may also result from the action and interaction of multiple ectopic impulses, and (b) the coexistence of a complete auriculoventricular block (for example in digitalis intoxication) will give rise to a regular heart beat in the face of the auricular disorder. The *direct* demonstration of auricular fibrillation (other than by inspection in open chest experiments or during operations) depends on the graphic demonstration of the disturbed auricular function by pulse tracings or by the electrocardiogram. In these, evidence of coordinated auricular activity is replaced by rapid irregular undulations of the base line with various and simultaneous frequencies ranging from 300 to over 1000 cycles per minute. It appears that individual cell units maintain their characteristic properties, displaying membrane, and action, potentials with depolarization and recovery in a reasonably orderly manner.[2] It is likely, therefore, that initiated by the electrical events, small areas of auricular tissue will undergo mechanical contraction and relaxation ("microsystole" of Wenckebach, "functional fragmentation" of Lewis). These are incoordinate and incoherent and, therefore, of no mechanical consequence as far as propulsion of blood is concerned: the auricles are in functional diastole. The disorder may be described as an "auricular dysrhythmia," to borrow a neurologic phrase.

Auricular flutter, on the other hand, clearly represents a rapid series of coordinate auricular contractions that are mechanically effective. Systolic auricular contractions and diastolic relaxation may be demonstrated by fluoroscopy, kymo- and electrokymography. The condition first observed in man by Ritchie (1905)[3] and by Hertz and Goodhart,[4] was clearly described by Jolly and Ritchie in 1910.[5] The recognition of this disorder at the bedside is difficult. It may become indistinguishable from auricular fibrillation if the ventricular rate is irregular. At regular rates, the steplike increase in rate on exercise or decrease on carotid sinus pressure with a temporary complete irregularity during the rising or falling phase in the ventricular rate is characteristic.[6] Again, the direct demonstration of auricular activity is essential for the diagnosis either by direct inspection of the jugular veins displaying the transmitted auricular waves or by graphic methods.* The electrocardiogram of auricular flutter displays ceaseless, uniform, rapid activity of the auricles varying from 250 to 350 beats per minute in untreated subjects. Auricular flutter, though occasionally maintained for years, is usually an unstable condition: a slight increase in the driving rate of the auricles causes a notable mechanical and electrical auricular irregularity, clearly intermediate between fibrillation and flutter ("impure flutter"). Slowing of the flutter rate, for in-

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* The presence of auricular sounds in flutter, first mentioned by Lewis,[28] may be termed an "auricular gallop." In many, if not all, instances they are to be considered extracardiac in origin and, like the systolic click (systolic ventricular gallop) are presumably caused by pleuropericardial adhesions. At any rate, they are not likely the result of vibrations set up in the fluttering auricle and since they occur during ventricular systole, are not caused by the inrushing blood pounding against the ventricular wall. They are therefore, very different from true ventricular gallop rhythms and from the ventricular sounds caused by auricular contraction in complete A-V block.

stance by quinidine or Pronestyl, results in electrocardiographic complexes that resemble normal P waves with definite isoelectric (that is, quiet), interauricular intervals. This type of record has recently been redescribed as "paroxysmal tachycardia with A-V block."[7] A clear differentiation between this disorder and regular flutter may be difficult, but since there are certain unresolved pharmacologic differences between them, it seems unwise at present to consider them identical and the terms interchangeable, as Prinzmetal proposes.[8] Nevertheless, the gradual transition from single ectopic beats to paroxysmal tachycardia to auricular flutter and to auricular fibrillation, first stressed in general terms by Hering in 1900,[9] can frequently be observed in one and the same patient. The undoubted inter-relationship between these irregularities is of no particular value in elucidating the nature of the dysrhythmia.

In recent years, a few advances in electrocardiographic technics have been made that are of some concern to the clinical evaluation of the auricular irregularities. Due to the proximity of certain precordial regions (third and fourth intercostal space at the right sternal border) to the auricular mass, so called unipolar leads from this area (V_1 position or one intercostal space higher) demonstrate auricular activity far better than the standard bipolar limb leads, although the *direction* of the spread of auricular excitation is still best demonstrated in leads I and II (excluding esophageal exploration). As far as P waves are concerned, these leads are not, however, directly comparable to direct leads from the cardiac surface and do not lend themselves easily to accurate measurements of the direction that an impulse assumes over auricular tissue. On the other hand, the use of esophageal leads, at a level of 30 to 40 cm. from the teeth, and of endocardial electrocardiograms places the exploring electrode in close proximity to the auricular musculature and permits an accurate tracing of the spread of auricular excitation. Such leads demonstrate the fundamental pattern of a surface electrogram of muscle tissue with a distinct multiphasic QRS-type deflection (P_{QRS}). The maximum positivity recorded by the exploring contact (the peak of P_R) closely coincides with the arrival of the impulse at the explored site. This point (the peak of the auricular R wave) has been termed by Lewis the onset of the "intrinsic" deflection, and its usefulness for estimating the time course of an action current as a tool in general electrophysiology considerably antedates Lewis' experiments. Its value cannot be disputed as long as measurements of the onset of the intrinsic deflection are confined to direct leads from the surface of the heart or leads reasonably similar to them (semidirect leads).

In auricular flutter the individual components of the flutter cycle, as seen in such semidirect esophageal or endocardial leads, differ in no important aspect from the auricular complexes during normal sinus rhythm, another indication of the orderly manner in which individual units pass in and out of the excitatory state, and a demonstration that the differences in the configuration of the P in standard limb leads in flutter as compared with paroxysmal tachycardia and normal rhythm are more apparent than real. In auricular fibrillation the demonstration of an intrinsic auricular deflection can usually be made only from endocardial leads. Clinical auricular fibrillation and auricular flutter have, therefore, become accessible to detailed electrophysiologic analysis which until recently was confined to animal experiments.

The Nature of Auricular Fibrillation and Auricular Flutter in Man

Cushny in 1899,[10] and, 10 years later, Rothberger and Winterberg[11] and Lewis[12] were the first to stress the similarity between the clinical syndrome of perpetual cardiac irregularity and the disorder following rapid electrical stimulation of cardiac tissue in dogs, first studied in Ludwig's laboratory and later extensively analyzed by McWilliam.[13] The overt identity of these two conditions has been accepted, and the results concerning the possible mechanisms of experimental auricular disorders following faradic stimulation, topical or intravenous application of aconitine, acetylcholine, barium chloride, fagarine, veratrine, and other substances in the experimental animal have been

transferred—perhaps too readily—to the spontaneously occurring disorder in man.

Over the years, three etiologic concepts have found widespread support: (1) *Multiple heterotopic impulse formation*, which assumes a complete, functional independence of small areas each responding to its own abnormal impulse center;[9, 12, 14, 15] (2) *single heterotopic tachysystole*, by which a single ectopic auricular focus of high inherent frequency will discharge repetitively and, therefore, act as auricular pacemaker;[8, 16, 17, 18] (3) *circus movement*,[19-24] where either one impulse traverses auricular tissue in a circular fashion with tangential offshoots (Lewis), or where multiple small circuits may be established.[19, 21]

The first concept (multiple ectopic foci), championed for many years by Lewis, is so closely related to the second that a clear separation of both need not be considered once it is assumed that each center may act as pacemaker by virtue of its frequency. It was based on Engelmann's original assumption that an increase in excitability of cardiac musculature preceded the onset of fibrillation. It was generally abandoned when it became obvious that a decrease in excitability was an important factor in the causation and maintenance of the disorder. The second and third concept have been considered—perhaps again without full justification—as mutually exclusive, with the British school largely proposing some form of circular excitation, and the Viennese school holding out for a unicellular (?) ectopic focus. Recent experimental work by Rosenblueth and his group, and on the other hand, by Scherf and by Prinzmetal and their associates have renewed the discussion which may be of practical importance from a therapeutic standpoint. The pharmacologic implications of the nature of these and related disorders have recently been presented admirably by Dawes.[25]

Is a Circus Movement Possible in Excitable Tissue? Yes

A circus movement (that is, re-entry of an impulse into an area of tissue that had responded to the same excitation wave before) is an experimentally proven fact. "If a closed circuit of muscle is provided . . . it is possible to start a wave in this circuit which will continue to propagate itself round and round the circuit for an indefinite number of times."[19] Such a cyclic recurring impulse propagation has been demonstrated for the following tissues: muscular ring of the jelly fish,[26] cardiac musculature of the turtle,[19, 20, 26, 27] heart of the electric ray, and frog,[19, 23] and large marine loggerhead turtle.[21] Common to all these experiments was the simplicity in design of the experiments which allowed the direct demonstration of the "merry-go-round" of either a contraction wave[19, 21, 26] or of an excitation wave.[19, 23] Furthermore: Two conditions were always present in these experiments: (1) the wave of excitation or contraction was always smaller than the circus path, and (2) the conduction of the impulse or the contraction was forced to proceed in one direction only. This was accomplished by preventing the natural bidirectional spread from the point of stimulation over both limbs of the circle through clamping or otherwise temporarily impeding conduction of a region adjacent to one side of the stimulus point. Thus, an impulse will be prevented from entering one limb of the path but can freely proceed over the other. It will eventually reach the obstructed area, arriving there from the opposite side, and, if the obstruction has by now been released and the tissue has become responsive again, the impulse will traverse through the previously clamped region to the point of origin (the site of the original stimulation), pass beyond this and continue perpetually over the prescribed circus path. Of particular interest in these earlier experiments are the observations by Garrey[21] that (1) during repetitive stimulation several such "circus contractions" followed each other, one upon the heel of the other, and that (2) local areas of refractory tissue caused the apparently complete disappearance of the circus contractions, only to have these reappear beyond the blocking area. Garrey assumed that these phenomena were created by failure of conduction in superficial muscle layers forcing the circus contractions through deeper layers from which they emerged beyond the obstructed region.

The important feature of these experiments

is the presence of local differences in the length of the excitatory state and, therefore, in the refractory period resulting in an unequal rate of tissue recovery which is delayed in one limb beyond the time interval separating repetitive stimulating impulses and thereby forces impulse conduction in one direction only. This phenomenon was later shown for heart muscle strips of the turtle by Schmitt and Erlanger[27] who demonstrated the presence of unidirectional impulse conduction and proved it to be a state of conduction impairment preceding complete blockage. Re-entry on this basis, and, therefore, circus movement, is possible even in longitudinal muscle fibers providing they have a certain width: fibrillation is not possible in narrow muscle bridges[21] and for this reason fibrillatory activity is not conducted from auricle to ventricle across the A-V bundle.

McWilliam, Mines, Garrey, and Erlanger all commented on the possibility that such mechanisms may be at play in certain types of extrasystolic disorders, paroxysmal tachycardia, and in fibrillation of the auricles and ventricles. We know that the mammalian heart in situ responds to the same fundamental laws as other excitable tissues. The experiments cited were conducted under artificial circumstances, but their results suggest that re-entry phenomena with consequent circus movement is a mechanism likely to occur in the human heart under appropriate circumstances.

Has a Circus Movement Been Demonstrated as the Cause of Clinical Auricular Fibrillation and Flutter? No

Sir Thomas Lewis, by inductive reasoning and by a series of limited, now classic, experiments attempted to apply the experimental results of Mines and Garrey to the mammalian heart and to clinical auricular fibrillation and flutter. He traced the excitation wave in electrically induced flutter in dogs by measuring the time interval between the summit of P in lead II and the intrinsic deflection of a direct auricular lead from the exposed heart. The results seemed to him to indicate that in flutter a circus movement would travel around the two venae cavae and that tangential offshoots from the "mother wave" would excite the remainder of auricular and ventricular muscle. A similar, but smaller circular pathway, perhaps around one vena cava only, would account for the basic mechanism of auricular fibrillation. The paths measured were not always in the same region: "In some instances. . .the wave would appear to circulate, not around the cavae, but in some other ring of muscle, such as that surrounding the mitral orifice; the events vary to this extent."[28] An additional point deserves emphasis: his measurements revealed an early completion of activation of the "auricle as a whole" during the upstroke of P in the normal heart: "activation is crowded into a very limited phase of the auricular cycle," while in auricular flutter ". . .the times of activation are diffused over the whole curve" of the auricular flutter cycle. Since in his experiments the exposure of the left auricle was poor, no direct measurements could be made over a large segment of the proposed circus path. Knowing the conduction velocity, Lewis was forced to calculate the spread over this "blind area" and to estimate the time of arrival at the next measurable point (inferior vena cava). His calculations coincided with the measurements obtained.

In one human subject with auricular flutter, calculations of the instantaneous electrical axes of the flutter cycle obtained in the sagittal plane demonstrated clockwise rotation through 360 degrees for each auricular complex.[29] Lewis recognized the limitations of his carefully conceived experiments but apparently thought that the many, to him interdependent, observations would support his conviction that all instances of auricular flutter and fibrillation were due to a circus movement. Rothberger very soon called attention to the limited number of experiments upon which Lewis' structure had been erected[30] and objected to the generalizations made from isolated experiments. He criticized the observations on the human heart on the ground that a relatively small circus path could not possibly dominate the auricular surface electrocardiogram and that the calculated axes would have to represent the instantaneous vectorial forces of the entire auricular mass. Lewis' conclusions from this

example appear certainly invalid since he, in effect, traced the auricular vectorcardiogram in the sagittal plane. As the vectorial forces of normal auricular and ventricular excitation describe a "loop" in space, it is only of interest that the same general order of excitation was present in his subject—an argument more against than in favor of a circus movement and, at any rate, simply an indication that the larger part of auricular tissue was activated in a straight sequential order, a point Lewis did not deny. Similar criticism applies to recent arguments based on like measurements by Decherd, Ruskin and Herrmann.[31]

The second observation on Lewis' case, the long duration of the auricular excitation in flutter as compared with the duration during normal sinus mechanism seems also to be fallacious. The statement that the "activation of the auricle as a whole. . .is crowded into a very limited phase of the auricular cycle" is illogical and apparently neglects the activation of the left auricle. It is evident that activation of the *right* auricle is crowded into the "upstroke and summit of P," but this is followed by the activation of the posterior and left auricular mass, obviously accounting for the remainder of the auricular deflection.[32] There seems to be no difference in the length of the excitation of the total auricular mass in the normal as compared with the fluttering auricular muscle.

Recent reports by Grishman and his coworkers[33] and by Cabrera and Sodi Pallares[34] have attempted to circumvent these earlier difficulties. Grishman's observations are not available for review, and the circus movement demonstrated by Cabrera and Sodi Pallares suffers from the fact that no definite intrinsic deflection can be obtained for auricular tissue in normal rhythm, as well as during auricular flutter, from the precordial region, presumably because the sheetlike auricular tissue is too far removed from the chestwall to allow the recording of truly semidirect leads.[32] The combination of endocardial and esophageal leads recently explored by Wenger and Hofman-Credner,[35] though again measuring only a portion of the path traversed by the impulse, seemed likewise to support the concept of a circus excitation. These observations are in direct contrast to Prinzmetal's published reports on human auricular flutter.

Lewis' experiments on the exposed auricle of the dog in flutter are of a more direct kind. Prinzmetal has republished one of Lewis' figures in order to demonstrate that the measurements of the proposed circus path were incomplete. This is true, but Prinzmetal did not show the companion figure depicting measurements obtained from the same preparation when the auricles were driven at a slow rate from a point close to the inferior vena cava, which in the flutter experiments was used as the reference point for zero time. When both illustrations are compared, it can be seen that in the normally beating auricle two points a few millimeters apart were activated within 0.014 second and 0.016 second after stimulation. In auricular flutter, when the previous point of stimulation was used as reference, the identical point to the right underwent excitation at 0.031 second (the delay in conduction being the result of the well known decrease in conduction velocity at rapid auricular rates), the identical point on the left at 0.137 second, or ten time later than expected. This, of course, Lewis explained as evidence that the impulse was delayed in reaching this area because it traveled over almost the entire circus path before reaching it from the opposite side, the time lag being consistent with the distance traversed. That this region was excited from two different directions, depending on whether flutter or sinus rhythm was present, was demonstrated by the direction of the steep excitation deflection recorded from paired electrodes placed over this area. In this one example of induced flutter and in four similar experiments a circus movement was likely to be present. Supporting experimental evidence for the presence of a large circus path in auricular flutter was recently advanced by Rosenblueth and Garcia Ramos[24] who have introduced a new method of maintaining auricular flutter by crushing the muscular bridges between the venae cavae thus creating an artificial obstacle around which the impulse may circulate perpetually. Their method is rapidly becoming a standard procedure for inducing a maintained flutter in animals. It strongly supports Lewis' experiments.

Has a Rapid Ectopic Focus (Heterotopic Tachysystole) Been Demonstrated as the Cause for Clinical Auricular Fibrillation and Auricular Flutter? No

The opponents of the theory of circus movement have presented impressive experimental evidence which favors the opinion that at least certain types of the auricular disorder may be the result of rapid repetitive impulse formation arising from a localized focus (tachysystole). For the disorders following faradic stimulation this was first demonstrated by Rothberger and Winterberg.[11] Lately, the topical application of various toxic agents notably acetylcholine, veratrine, and aconitine have been employed to induce auricular fibrillation and flutter in dogs. In a large series of experiments, Scherf and his co-workers have demonstrated that the arrhythmia induced by these agents may be blocked by local cooling, vagal stimulation, or stretching, only to reappear gradually when these procedures were discontinued.[37-41] Flutter induced from a focus in the auricular appendage was abolished by clamping the muscular connections to the main auricular mass. It is of considerable interest that cooling was effective in blocking the aconitine-induced disorder but not the outwardly similar irregularity caused by faradic or rhythmic electrical stimulation or by the application of acetylcholine.[41] Prinzmetal and his co-workers have presented an equally formidable body of evidence demonstrating that under their experimental conditions no gross circus movement was evident, and that destroying the intercaval area had no effect on the disorder, an observation in direct contrast to Rosenblueth but previously reported also by Brams and Katz.[42]

The inference from these experiments, largely based on irregularities induced by the topical application of toxic agents, is, of course, that (1) no circus movement was observed, and (2) that spontaneous auricular fibrillation and flutter are also caused by a local focus. It is impossible to assess whether the jump to this conclusion is justified or whether the auricular dysrhythmia may not be the end result and the visible expression of various mechanisms. The different behavior to cooling of variously induced auricular fibrillation led Scherf to the statement "that we are not justified in considering fibrillation to be due to a single mechanism."[41] The visible blocking of such disorders by cooling or clamping cannot be considered incontestable proof against a circus movement since it has been noted in undoubted circus contractions in turtle muscle strips by Garrey. Prinzmetal's actual measurements of the path of excitation in aconitine-induced flutter in dogs seems to rule out a circus movement effectively in his experiments. His observations on the human heart, however, are confined to measurements obtained from either esophageal leads or precordial points and are less conclusive since the path pursued by the auricular excitation wave could be followed only over a limited distance.

Since re-entry is possible in excitable tissue, the occurrence of many circus movements of very much smaller dimensions arising in damaged tissue and traversing the syncytial cardiac muscle in an eddy-like fashion remains a theoretic possibility, even if a large circular path in Lewis' sense should prove a rare occurrence. It might be assumed that the focus itself, and the area surrounding it, stimulated by agents and procedures known to alter conduction velocity and refractory period, might consist of damaged fibers in which excitation re-enters continuously. These possibilities are not excluded in Scherf's and Prinzmetal's experiments and are at present beyond the scope of experimental verification. Finally, a small repetitive focus, a large circular excitation with tangential offshoots, and small reverberating waves of re-entry may all have a place in the production and maintenance of the clinical syndrome of auricular fibrillation and auricular flutter.

Since the completion of the manuscript an experimental paper by B. B. Brown and G. H. Acheson has appeared in Circulation,[43] comparing certain characteristics of aconitine-induced irregularities with those obtained by rapid electrical stimulation. The two "flutters" responded differently to various agents and could be observed simultaneously in one auricle. These observations support the concept that several mechanisms may give rise to similar clinical events, as has been outlined.

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The Mechanism of Auricular Flutter and Auricular Fibrillation

By Louis N. Katz, M.D., and Alfred Pick, M.D.

THE renewed interest in the mechanisms underlying the various types of auricular arrhythmias stems primarily from the development of new methods of experimental approach. Electrical stimulation used by the majority of previous investigators to induce disturbances of auricular activation was known to effect auricular arrhythmias of only short duration, often restricted to the time of stimulation. Hence, the first fundamental step for further investigations was Scherf's publication in 1947[1] of a simple method to produce auricular arrhythmias of almost unlimited duration by application of aconitine to the exposed auricle of the dog. The method itself, and the first results of its use, developed into a serious challenge of apparently well established concepts[2] almost universally accepted in the Anglo-American literature. The method, then, proved particularly useful in experiments performed with improved technics of exposure of both auricles and with highly developed technics of observation of the disturbed auricular function, as introduced by Prinzmetal.[3] However, while this new experimental approach seemed to weaken the fundamental concept derived from the basic experiments of Lewis, new evidence in its support was provided by the work of Rosenblueth and his group.[4-6] These and other controversial data of the past[7, 8] were a great stimulus toward reopening the discussion.

The Principal Theories of Continuous Rapid Activity of the Auricles

In discussing this problem the first step is to present the theories which have been advanced for these rhythms. The principal ones are:

I. The theory of *multiple foci* with rapid discharge, first advanced by Engelman,[9] was favored originally by the Viennese school[10] and utilized as an explanation of fibrillation up to the present by Kisch.[11]

II. The theory of a *single ectopic focus* with rapid discharge was advocated by Rothberger and Winterberg[12] and by Scherf as a result of his first experiments with aconitine[13] and accepted by Prinzmetal.[3]

III. The theory of a *single circulating wave* was conceived by Lewis,[14, 15] and in a modified form by De Boer.[16] A related concept has been advanced by Ashman[17] and Barker and co-workers[18] to explain the mechanism of supraventricular tachycardias other than auricular flutter and fibrillation.

IV. The concept of *multiple and minute re-entries* of the wave of excitation, was proposed by Garrey[19] and also applied by Wiggers[20] in his studies on ventricular fibrillation.

V. The concept of *multiple self sustained microsystole* with "extreme reduction of consumption of systolic energy" was advanced by Wenckebach and Winterberg.[21]

The numerous arguments which have been brought forward in favor of and against each of the above concepts have many aspects in common. Their essential points can be summarized in connection with the following three salient questions:

1. *Has re-entry and circus movement been proved in the heart of experimental animals and of man? Can such a mechanism alone account for the development of auricular flutter and fibrillation?*

Re-entry and continued *slow* circulation of the cardiac impulse has been demonstrated beyond question by Mines[22] and Garrey[19] in excised parts of the auricles and ventricles of experimental animals. Incomplete evidence of its *rapid* form was provided by Lewis and co-workers[23] in their attempts to trace the path-

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way of the wave of excitation in experimental auricular flutter. Objections to the latter were raised very soon by Rothberger[24] who pointed out the lack of continuous muscular structures within the narrow pathway as supposed by Lewis. However, the argument that Lewis was unable to trace the wave of excitation over its entire pathway around the venous ostia became invalid when unquestionably complete circuits of the impulse in the auricles around artificial obstacles of sufficient perimeter and completely surrounded by conductive tissue were demonstrated by Rosenblueth and coworkers.[5, 6] Further and important arguments against a single mother wave initiating auricular fibrillation and flutter can be considered to be the experiments of Brams and Katz[8] who observed the persistence of both types of arrhythmia in both parts of the chamber following complete separation of the auricle into two parts, and similar observations of Prinzmetal[3] following scarification of the region of the supposed pathway of Lewis' mother wave.

Lewis also believed that evidence for a circus movement in human auricular flutter could be derived from the rotation of the electrical axis of auricular activation constructed from three-dimensional chest leads.[25] His calculations performed in only a few patients with auricular flutter were later confirmed by others[26] with a larger amount of material and recently amplified with the help of similar analysis of simultaneous esophageal and intracardiac leads in patients with auricular flutter and fibrillation.[27] However, as far back as 1923, Rothberger had stressed the weakness of the argument by pointing out that the auricular complex (*F* wave) in auricular flutter necessarily represents the activation of the entire mass of both auricles taking place in all directions, rather than the reflection of electrical phenomena associated with the activation of a narrow muscle band around the venae cavae, as supposed by Lewis. Prinzmetal, after repeating Lewis' calculations, came to the conclusion that the diphasic character of auricular complexes in flutter is a manifestation of both auricular depolarization and repolarization occurring in rapid alternation. Such a concept, invalidating one of Lewis' principle arguments, seems convincing particularly in view of similar events taking place with the onset and progressive acceleration of ventricular tachycardias, resulting eventually in the typical see-saw appearance of the electrocardiogram. The same author also failed to observe in high-speed-camera motion pictures, even under high magnification, any type of motion which would suggest a circulating movement in the fibrillating auricles of dogs and of man.[3]

While, thus, no direct evidence is at hand which would prove the existence of a circulating type of movement in *human* auricular flutter and fibrillation, proof for re-entry of the cardiac impulse in other than auricular tissue is available. A considerable number of unquestionable clinical instances of reciprocal beating has been reported. Recently[28, 29] repetitive and multiple re-entry of the cardiac impulse within the A-V node was strongly suggested on the basis of a detailed analysis of electrocardiograms in clinical instances exhibiting complex, rare and otherwise unexplained arrhythmias.

2. Is there sufficient evidence for the presence of one or more rapidly firing foci which would account satisfactorily for the development of auricular flutter and fibrillation in the experimental animal and in man?

Undoubtedly, the strongest point of evidence in this respect is the fact that all three types of rapid auricular arrhythmias—tachysystole, flutter, and fibrillation—and transitions of one into the other, can be produced experimentally by *focal* application of an electrical or pharmacologic stimulus to the auricle. Further and even stronger support is provided by the fact that at least tachysystole and flutter can be acutely stopped by cooling the initiating focus or separating it from the rest of the auricle, and by the prompt reappearance of rapid auricular activity by rewarming the area of the focus.[1] While all these observations appear, at first glance, to be incompatible with the circus movement theory, consideration of additional experimental data and of clinical experience is apt to prevent unconditional acceptance of this mechanism as the sole responsible factor for the development of all types of rapid auricular activity as proposed

by Prinzmetal in the form of his concept of the "unitary nature of auricular arrhythmias."[3] Very early in the course of such an investigation, it was pointed out by Garrey that following division of the fibrillating auricles into two and even four equal parts, each of them persists in its uncoordinated and rapid activity.[7] Experiments on fibrillating and fluttering auricles and ventricles, with identical results, were reported later by Brams and Katz.[8]* Furthermore, it has been repeatedly shown that experimental auricular or ventricular fibrillation can be induced by a single induction shock applied in a certain "vulnerable" time period at the beginning of the repolarization of the respective chamber, and this mechanism can also be terminated by a similar procedure.[20, 30] Such facts are hard to reconcile with the concept of a pure "unifocal" theory of the mechanism of this disturbance of rhythm.

Further objections against any "focal" origin of auricular arrhythmias stem from pharmacologic and clinical experience rather than from direct evidence. This refers mainly to the different response of simple auricular tachysystole on one hand, and auricular flutter and fibrillation on the other hand, to (1) vagal stimulation, (2) treatment with digitalis, (3) their abrupt onset and termination and (4) their failure to recur clinically after interruption. Also, the persistence of one or more foci of rapid impulse formation over many years and the necessarily associated shortening of the refractory phase over long periods of time are inconsistent with known physiologic facts.[7, 17] Such considerations forced some authors[17, 18] to invoke mechanism of a circus movement not only for flutter and fibrillation but also for other types of supraventricular tachycardias.

3. Is there reason for, and the possibility of, reconciling the two divergent standpoints?

As outlined in the preceding paragraphs none of the proposed theories—single or multiple circus movements, single or multiple rapidly discharging foci—can by itself apparently account for *all* the diverse phenomena associated with the *appearance*, *perpetuation* and *termination* of auricular flutter and fibrillation produced experimentally or observed in clinical instances. Therefore, the logical question arises whether a compromise standpoint could contribute to the solution of the unsolved problem. Attempts in this direction are not wanting in the writings of past and present investigators. Wenckebach and Winterberg have pointed out in their monograph[21] that once a point of re-entry has developed in excitable tissue it can be considered as a focus firing rapid impulses in all directions. Rothberger in his discussion of the genesis of ventricular fibrillation[31] visualized the chain of events as follows: An initial single focus discharging impulses at a high and regular rate effects in the surrounding myocardium progressive shortening of the refractory period, and at the same time a progressive decline of conductivity; thus conditions are created favorable for the development of local re-entries of the impulses. While this is at first restricted to an area around the point of impulse formation, the same process could suddenly extend over the whole affected chamber with the result of innumerable minute re-entries, each of them discharging impulses in all directions and terminating in a condition of more or less uncoordinated activity, termed fibrillation. A similar mechanism was suggested by Scherf[13] to be operating in auricular arrhythmias. It is perhaps of interest that Scherf, originally a decided proponent of a unifocal theory of the mechanism of all three types of auricular tachycardias, concluded as a result of later experiments[32, 33] that a rhythmic stimulus may be acting in auricular tachycardias and a continuous stimulus in auricular flutter and fibrillation; he further concluded that fibrillation cannot be due to a single mechanism. According to his more recent view, Scherf believes a circus movement is not the cause but a concomitant feature of rapid auricular activity.

Personal Opinion

This opportunity to resurvey the literature has not materially altered the viewpoints expressed previously, after a similar survey in

* Prinzmetal, in order to support his concept, performed similar experiments with his technics but unfortunately fails to state whether fibrillation persisted in *both* parts of the separated auricles.[3]

1946.[34] Auricular flutter and fibrillation is initiated by a single impulse coming in a vulnerable period of the heart cycle. This may be a sinus impulse when the heart's function is markedly depressed, or a premature ectopic one when the heart is less depressed. Thus, the degree of prematurity of the impulse sufficient for perpetuation of the disturbance of rhythm will vary more or less inversely with the impairment of the heart's functions particularly with the prolongation of the refractory phase. Of course, a continued acceleration of the sinus pacemaker, or of a rapid ectopic one, may help to sustain auricular flutter and fibrillation once it is initiated. Hence, in certain instances, depression or abolition of an ectopic focus will permit auricular flutter or fibrillation, sustained by its activity, to disappear. In addition, the borderline between a rapid tachysystole with radial spread of the impulse and a rapid auricular activity giving rise to the peculiar phenomena of flutter is a variable one depending on the functional state of the auricle at the time. In other words, not every tachycardia of the auricle at a rate of 300 or more is flutter (or fibrillation) even though the waves expressing auricular activity occupy the entire auricular cycle. As has been mentioned this may merely mean that both auricular depolarization and repolarization are electrically manifest.

It would seem that the perpetuation of auricular flutter and fibrillation depends on the development of multiple re-entries. In flutter, the cyclic repetition of these re-entries is practically fixed in pattern. In fibrillation, no fixed pattern for the repetitive re-entries exists and in impure flutter there is some tendency to a fixed pattern, but this is imperfect. By use of such a concept the beautiful studies of Lewis and his associates, referred to earlier, can be applied, not as Lewis did in oversimplifying the subject to a mother ring, but rather to the multiple simultaneous circulating waves, each with its "gap" and its "head" trying to reach and swallow its "tail." In this fashion, the arguments of the "circus movement exponents" can be accomodated without the need of locating a *primary circulating wave*.

The conditions for re-entry are ripe in the auricular syncitium provided only that an impulse can come early enough in the refractory phase so that it reaches a point of branching while one arm is still refractory and prevents its passage, and the other arm is not. Under these conditions the impulse will travel through a loop, short or long, and return to the point of branching in a retrograde fashion. If, now, this branching is no longer refractory the impulse will re-enter the myocardium. Since the path is usually short, the re-entering impulse will be very premature and this, in turn, will enable it to set up re-entries in neighboring regions, and so re-entries will pile up, spread over the auricles, and perpetuate themselves. The ease of setting up re-entries is obviously facilitated in the case of diseased auricles for several reasons. First, the refractory period is prolonged by disease making it possible more often for the impulse to reach points of branching in which one limb is refractory and the other is not. Second, the effect of disease is to make the functional state of neighboring parts of the syncitium more unequal so that the frequency with which the impulse encounters loops ripe for re-entry is enhanced. Third, the sort of state established experimentally by Rosenblueth and his co-workers is more apt to occur; such states can be due to anatomic changes or to functional ones following upon ischemia, hypoxia or altered states of the innervation, or of electrolyte balance.

It would follow from the above that the more diseased the auricles are, the less premature need be the impulse initiating and/or sustaining the mechanism of multiple re-entries responsible for flutter and fibrillation, the greater also the ease of the re-entries perpetuating new re-entries, and the smaller the chance to overcome the mechanism pharmacologically. The saving grace for the last, however, is the fact that improving the physiologic state of the heart handicaps the facility of re-entries to continue. To this can be added the fact that drugs which "close the gap," as established by the school of Lewis, also offer a positive approach to the handling of these important clinical entities.

It must be stated in conclusion that this personal opinion is merely the working hypothesis of the authors and in no sense an

established fact. Time alone will offer the ultimate solution, but we predict that auricular flutter and fibrillation will turn out to be more complex than is suggested by any unitary theory. Moreover, it should be kept in mind that the experiments used in evidence are performed on animals for the most part with normal hearts whereas clinical auricular flutter and fibrillation develops in patients with heart disease. So far, nobody has been able to reproduce in animals conditions which would approximate all anatomic and functional alterations present in diseased human hearts with auricular flutter and fibrillation. Thus, experimentally produced disturbances of cardiac rhythm, and the mode of their production, may not be identical with seemingly similar events occurring under certain pathologic conditions in man. Structural and/or biochemical factors, not known or so far not suspected, may precipitate, or facilitate, the development of various types of auricular arrhythmias in man. There remains for the future this matter of correlation of further experimental and clinical investigations.

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The Mechanism of Spontaneous Auricular Flutter and Fibrillation in Man

By Myron Prinzmetal, M.D.

ALTHOUGH auricular flutter and fibrillation have been studied for many years, most evidence obtained is relatively indirect and subject to various interpretations. Consequently, considerable controversy exists concerning the mechanism of these arrhythmias. Of the various investigative methods now available, only two provide definitive evidence of the exact course of events occurring in the auricles. First, the auricular excitation wave may be traced by means of direct or semidirect leads from multiple sites on or adjacent to the auricular surface. Second, the auricular contraction wave may be clearly visualized in high-speed cinematographs. As described elsewhere, these two direct methods of observation have been extensively employed in experimental animals. More recently, the operations of auricular appendectomy and mitral commissurotomy have enabled us to observe directly the auricles of several patients during episodes of spontaneous auricular flutter or fibrillation. Further studies of spontaneous arrhythmias in man are now in progress and will be reported fully in subsequent communications.*

In the experimental animal, auricular flutter and fibrillation may be initiated by a variety of methods. The possibility exists that flutter or fibrillation produced by one method may differ in mechanism from examples of the same arrhythmia produced by an alternative method.† Moreover, it has been contended that experimentally produced flutter and fibrillation in animals may involve different mechanisms than their spontaneous counterparts in man. Since the experimental findings are of widespread interest only insofar as they elucidate clinical disturbances, the present discussion will be limited to (1) a description of electrocardiographic and cinematographic observations in patients with spontaneous flutter or fibrillation, and (2) a brief comparison between observations in man and experimental animals.

Clinically, auricular flutter and auricular fibrillation are closely associated. Both arrhythmias commonly accompany the same disease states. Moreover, conversion from flutter to fibrillation or from fibrillation to flutter often occurs either spontaneously or in response to drugs. Nevertheless, electrical and mechanical activity in the auricles of patients during spontaneous flutter has been found to differ radically from the activity characterizing spontaneous fibrillation. Observations on the two arrhythmias will therefore be presented separately.

Spontaneous Auricular Flutter in Man

The mechanism of spontaneous auricular flutter in patients was studied by the methods of simultaneous multiple esophageal lead electrocardiography, precordial and limb lead electrocardiography, and high-speed cinematography.

Electrocardiographic Findings.

At a distance of approximately 20 to 40 cm. from the lips, the human esophagus is in close association with both auricles. The esophageal

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* These observations have been made with Drs. Rexford S. Kennamer, Jack Bernstein, Alfred Goldman and Harold Karpman.

† Evidence has been advanced by Rosenblueth and Barbara B. Brown that a circus movement is present in auricular flutter produced by the crush method. No circus movement occurs when auricular flutter is produced by electrical stimulation, post-electrical stimulation or local application of aconitine.

region 30 to 37 cm. below the lips is at the midauricular level and is directly posterior to the interauricular septum. At the level of the extreme caudal end of the auricles, 37 to 40 cm. below the lips, the esophagus appears to be in more intimate contact with the right than with the left auricle. At levels 20 to 30 cm. from the lips, the esophagus is immediately posterior to the cephalic extremity of the left auricle. Although all portions of both auricles are not in direct contact with the esophagus, the distance separating these structures is so slight that electrical potentials in *both* auricles are recorded in esophageal leads from all auricular levels. Therefore, the course of the auricular impulse can be determined by analyzing the configuration of the depolarization waves in simultaneous esophageal leads. This has been accomplished in previous studies by other workers as well as in the present investigation of spontaneous auricular flutter in man.

Most patients with auricular flutter exhibit inverted depolarization waves in limb leads I, II and aV_F. In these instances, representing the "common type" of flutter, esophageal leads from the caudal level of the auricles display a purely negative depolarization wave, esophageal leads from the cephalic level of the auricles present a purely positive wave, and esophageal leads from the midauricular level contain a negative wave followed by a positive wave. In the uncommon type of auricular flutter, in which the depolarization wave is upright in limb leads I, II and aV_F, negative depolarization waves are recorded in esophageal leads from the cephalic level and positive waves appear in esophageal leads from the caudal level; esophageal leads from the midauricular level exhibit biphasic deflections similar to those observed in the common type of flutter. Interpretation of these tracings is based upon the fundamental electrocardiographic principle that a negative deflection is inscribed as the cardiac impulse travels away from the recording electrode, while a positive deflection occurs when the impulse is traveling toward the electrode; a pure negative wave (called the intrinsicoid deflection), is recorded by an electrode at or near the site of origin of the impulse.

By applying the preceding principle, the esophageal lead electrocardiogram of spontaneous auricular flutter may be interpreted as follows: In the common type of flutter, the purely negative deflection recorded from the caudal level indicates that the impulse arises at and travels away from the caudal region of the auricles. Conversely, the positive deflection obtained in esophageal leads from the cephalic level establishes that the auricular impulse travels toward and terminates in the cephalic region. The biphasic deflection from the midauricular level shows that the impulse travels toward the middle of the auricle, passes beneath the recording electrode, then recedes from the electrode as it continues its journey to the cephalic extremity. Since electrodes in the esophagus record potentials in both auricles, the auricular impulse in these instances must originate from a caudal focus and travel in a caudocephalic direction through both auricles simultaneously. In the uncommon type of flutter, the impulse must arise in the cephalic region and travel through both auricles simultaneously in a cephalocaudal direction.

If a self-perpetuating circus movement were present in auricular flutter, as originally hypothesized by Lewis, identical deflections would be expected to occur in esophageal leads from all auricular levels since the circular path would be without beginning or end. Hence the above findings are inconsistent with Lewis' concept of circus movement. If a circus movement arose anew with each cardiac cycle, as suggested by certain workers, the deflections in esophageal leads from various auricular levels again would differ radically from those described above. In the common type of flutter, an impulse pursuing a circus pathway through both auricles would travel from the caudal region of one auricle to the cephalic extremity, where it would enter the opposite auricle and travel in a cephalocaudal direction on its return journey to the focus. Under such circumstances, electrodes in the esophagus at the caudal level of the auricles would register a negative deflection as the impulse traveled toward the cephalic region, followed by a positive deflection as the impulse returned to the caudal region. Similarly, esophageal leads

from the cephalic level of the auricles would exhibit a biphasic deflection, consisting of a positive component recorded while the impulse traveled up one auricle and a negative component recorded during the return journey. Finally, an electrode at the midauricular level would register a positive deflection as the impulse traveled from the focus to the middle of one auricle, a negative deflection as the impulse passed the electrode and continued to the cephalic extremity, and a second positive-negative phase as the impulse traversed the opposite auricle. Equally complex deflections would be recorded in the uncommon type of flutter if a circus movement was present. Thus, assuming that the fundamental principles of electrocardiography are valid, the configuration of the depolarization waves in esophageal leads from patients with spontaneous flutter is entirely incompatible with the occurrence of a circus movement traversing both auricles. Moreover, the above findings are equally inconsistent with the existence of a circus pathway around the septum, within only one auricle, or involving any anterolateral portion of one or both auricles. A comparison of the times of onset of the intrinsicoid deflections in esophageal and precordial leads, as well as a calculation of the momentary auricular electrical axes in limb leads, likewise indicate that the excitation wave of spontaneous auricular flutter in man arises from an ectopic focus and pursues a linear rather than a circus pathway.

Certain patients with flutter arising from the cephalic region of the auricles exhibit depolarization (P′) waves virtually identical with the normal P waves in limb and esophageal leads; that is, both the normal P and flutter P′ deflections are upright in leads I, II, aV_F and esophageal leads from midauricular levels, and inverted in esophageal leads from high auricular levels. It is generally acknowledged that the normal P wave is a graphic representation of the course of the auricular depolarization wave as it spreads radially outward from its site of origin. Since the P′ wave of flutter sometimes is identical with the normal P wave, it is apparent that the flutter excitation wave in such instances likewise spreads radially from its site of origin rather than along a circus pathway.

Cinematographic Findings.

High-speed cinematographs of the exposed auricles have been recorded during mitral commissurotomy in a patient with spontaneous auricular flutter. Routine tracings from this patient exhibited inverted depolarization waves in limb leads II and III, indicating that the arrhythmia was of the common type arising in the caudal region. The auricular flutter rate was 240 beats per minute. Films were recorded at a camera speed of 100 frames per second and projected at a rate of 8 frames per second; hence the auricular contractions depicted on the screen were 13 times slower than the actual heart rate and occupied an interval of approximately 3.6 seconds per beat.

By pushing down on the pulmonary artery, it was possible to obtain films in which the motion of both auricular appendices was very clearly seen. If a circus movement had been present, either the left or the right appendix would have contracted before its fellow, depending on whether the movement were clockwise or counterclockwise. Indeed, assuming the distance between the two appendices constitutes one fourth of the hypothetic circus pathway, one appendix would have contracted about one second before the other. Actually, however, repeated examination of the cinematographs revealed that the two appendices contracted simultaneously. This phenomenon is entirely incompatible with the circus movement theory, but is consistent with the electrocardiographic observations described above. Cinematographically as well as electrocardiographically, therefore, it has been demonstrated that the excitation wave of spontaneous auricular flutter in man starts at an ectopic focus and spreads in a linear pathway through both auricles simultaneously.

Spontaneous Auricular Fibrillation in Man

Spontaneous auricular fibrillation in patients was studied by means of direct auricular lead electrocardiograms, esophageal and limb

lead oscillograms, and high-speed cinematographs.

Electrocardiographic Findings.

During operations on the mitral valve, direct auricular leads from four patients with spontaneous auricular fibrillation were recorded on the Sanborn Twin Beam Cardiograph. This photographic-writing instrument was operated at a paper speed of 75 mm. per second, yielding a much more accurate representation of the rapid electrical activity in the fibrillating auricle than is obtainable with standard electrocardiographic equipment. Examination of the tracings revealed slightly irregular waves varying from 0.2 to 0.4 mv. in amplitude and occurring at a frequency of 350 to 400 per minute. Some of the waves presented a sharp downstroke resembling an intrinsic deflection. No two waves were identical in shape or size. These deflections presumably correspond to the familiar "*f*" waves seen in limb leads of auricular fibrillation. In addition to the large waves, smaller waves of highly variable contour occurred at extremely rapid and irregular rates throughout the direct lead tracing, appearing as peaks or undulations along the baseline and on the upstroke and downstroke of the larger deflections.

Esophageal leads from 4 undigitalized and 20 digitalized patients with auricular fibrillation were recorded with the cathode ray oscillograph. Because of freedom from inertia, rapid recording speeds and virtually unlimited frequency response, the oscillograph proved even more satisfactory for purposes of the study than the photographic-writing cardiograph. In undigitalized subjects, esophageal leads from auricular levels revealed essentially the same phenomena as the direct leads described above. Large "*f*" waves, approximately 0.2 to 1.0 mv. in amplitude, were recorded at frequencies of about 350 to 600 per minute. Small waves, usually 0.1 mv. or less in amplitude, occurred at extremely irregular rates as high as several thousand per minute.

Simultaneous oscillograms from two electrodes placed 2.5 to 5 cm. apart in the esophagus revealed little or no synchronicity between the electrical activity in different parts of the fibrillating auricle. Esophageal leads from the digitalized patients exhibited deflections of much lower amplitude than records from undigitalized subjects but were otherwise essentially similar.

Cinematographic Findings.

High-speed cinematographs of the fibrillating auricles were recorded in four patients during mitral commissurotomy and in one patient during auricular appendectomy. Because of the presence of mitral stenosis, the left auricles of these patients were distended and often filled with clot; this factor, coupled with digitalization, limited the motion of the left auricle. However, in the patients undergoing commissurotomy, excellent cinematographs of the fibrillating right auricular appendix were obtained by pushing down the pulmonary artery.

When viewed in slow-motion pictures, the right auricular appendix was seen to contract at an irregular rate of 350 to 400 beats per second. Each contraction appeared as a more or less organized wave differing somewhat from the preceding wave in course, vigor, and rate of propagation. Careful examination of the films further revealed a second type of mechanical activity occurring simultaneously with the large contraction waves and consisting of rapid, heterorhythmic contractions and dilations of minute muscle segments throughout the appendix. These microscopic contractions were most readily discerned in the tip of the appendix where the fimbria twisted and turned first in one direction, then in another, in an entirely uncoordinated manner. Presumably the large contraction waves seen in the films correspond to the electrocardiographic "*f*" waves, while the microscopic contractions are mechanical counterparts of the small deflections recorded in direct leads.

Conclusions

From the preceding electrocardiographic, oscilloscopic and cinematographic observations, it may be concluded that spontaneous auricular fibrillation in the patient is a heterorhythmic disturbance composed of irregular large waves

which pursue a variable course over a sea of asynchronously contracting minute muscle segments. Neither the tracings nor the films reveal any evidence of a circus movement, or of an "isoelectric gap" or "daughter waves" such as those hypothesized by proponents of the circus movement theory.

Relationship between Clinical and Experimental Arrhythmias

Except for differences attributable to pathology and medication, the preceding observations on spontaneous auricular flutter and fibrillation in man are remarkably similar to findings obtained during a four-year study of experimentally produced auricular arrhythmias in dogs. Direct leads and high-speed cinematographs from numerous experimental animals have shown that auricular flutter consists of rhythmic waves traveling from a focus at one end of the auricles to the opposite extremity through both auricles simultaneously, and that auricular fibrillation consists of heterorhythmic activity comparable to the large and small waves recorded from the fibrillating auricles of patients. The existence of a circus movement in the experimental instances studied has been conclusively ruled out. Although the operation of mitral commissurotomy has greatly facilitated investigation of the human auricle, much remains to be learned concerning the relationship between clinical and experimentally produced auricular arrhythmias. Nevertheless, it is noteworthy that findings in a large series of experimental animals are essentially similar to the results obtained by direct observation of spontaneous auricular flutter and fibrillation in man.

The Mechanism of Auricular Flutter and Auricular Fibrillation

By ARTUO ROSENBLUETH, M.D.

A DISCUSSION of the mechanism of auricular flutter or fibrillation requires first a precise definition of what is meant by those terms. They were coined originally to designate more or less characteristic clinical syndromes, but they are now applied loosely to a heterogeneous group of experimental results that may bear only a superficial resemblance to those syndromes. Thus, it is possible to define flutter and fibrillation exclusively on the basis of rate, as was done recently by Prinzmetal and his associates.[4] This definition, however, is undesirable, because it groups together conditions which have quite different features; for example, it does not distinguish fast auricular activity that is stopped by acetylcholine from activity with the same frequency that is not stopped by acetylcholine.

As pointed out by Wiener and Rosenblueth,[7] the structure and properties of auricular muscle are such that they allow for at least two modes of recurrent activity. In the first, impulses start at one or several points, they spread through the muscle and disappear at its boundaries; recurrence cannot take place without reinitiation; we may designate these impulses as beats. In the second, an impulse travels continuously in one direction over a closed circuit and recurs cyclically because the front of the impulse meets always nonrefractory tissue; we may designate this activity as cyclically recurrent or circus movement.

That mammalian auricular muscle is capable of exhibiting automatic beats in the absence of connections with nodal tissue has been shown by Rosenblueth and García Ramos.[5, 6] Two different types of automatic activity were observed, a slow and a fast activity. The differences between the two types refer not only to rate but to other features, in particular to response to the action of acetylcholine. The suggestion that some of the clinical auricular dysrhythmias may be due to ectopic automatic foci has thus a sound experimental basis.

That mammalian auricular muscle may exhibit cyclically recurrent activity has also been demonstrated. The observations of Lewis, Feil and Stroud[3] strongly supported this thesis, and conclusive proof of the development of such activity in appropriate experimental conditions was furnished by Rosenblueth and García Ramos.[2] Multiple recording around an artificial obstacle allowed us to follow the temporal and spatial course of the impulses and made it clear that a single impulse was traveling unidirectionally around the obstacle in one or the other direction. The suggestion that some of the auricular dysrhythmias may be due to a cyclically recurring impulse has thus, in turn, a solid experimental basis.

The problem of the mechanism of auricular flutter and fibrillation is a clinical problem; that is, it can be answered only by studies carried out on patients that exhibit these dysrhythmias. An evaluation of these studies leads to the conclusion that, unless the human auricle differs importantly from that of cats or dogs, there are no data in favor of the view that these perturbed rhythms are due to the discharges of automatic foci. The only two autonomous auricular activities known so far are those described by Rosenblueth and García Ramos. The minimal rate of the fast activity is about 20 per second, much too fast even for auricular fibrillation. Flutter and fibrillation would thus be comparable to the slow activity, but this activity is promptly abolished by the injection of acetylcholine or by vagal stimulation, procedures that do not cancel the dysrhythmias in question.

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Prinzmetal and associates[4] have argued that flutter is due to ectopic discharges because its electrocardiogram is similar to that of hearts treated locally with aconitine, a drug that elicits repetitive discharges. The logic of this argument is faulty. The resemblance is entirely explicable on the basis of a gross correspondence of rate. The cyclically recurrent activity elicited by Rosenblueth and García Ramos also yields electrocardiograms that resemble those of flutter.

There are, on the contrary, many data in support of the thesis that both auricular flutter and fibrillation are due to cyclically recurring activity—i.e., to "circus movements" of impulses. Some of these follow:

a) As pointed out by Wiener and Rosenblueth,[7] in view of the conduction velocity of auricular impulses (0.4 to 0.5 meter per second), of the duration of the refractory period of the muscle (0.1 second) and of the rates of flutter (3.7 to 6.2 per second) and of fibrillation (6.7 to 10 per second), the appropriate perimeters of the obstacles involved, if these activities are cyclically recurrent, should be over 10 and 5.0 to 6.2 cm., respectively; the perimeter of the human inferior cava is about 9.7, and that of the superior cava, about 6.6 cm. The relative constancy of the rates of the dysrhythmias supports the view that these rates are determined not only by the physiologic constants, but also by the anatomic structure of the muscle. The common sequence, fibrillation → flutter → beats, is probably no accident.

b) Acetylcholine accelerates both flutter and fibrillation, much as it accelerates experimental cyclically recurrent activity by shortening the refractory period.

c) The study of the propagation of the flutter wave carried out by Cabrera and Sodi[1] showed a regular successive circular activation on the sagittal plane. These observations provide a direct proof of the cyclically recurrent characteristic of the abnormal activity in the patients they studied.

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ABSTRACTS

BACTERIAL ENDOCARDITIS

Hamburger, M., and Stein, L.: Streptococcus Viridans Subacute Bacterial Endocarditis. J. A. M. A. **149:** 542 (June 7), 1952.

Twelve patients with subacute bacterial endocarditis caused by penicillin-sensitive Streptococci were treated with daily administration of 15 to 16 million units of penicillin. The first few patients received their dosage intravenously. The remainder had intramuscular dosage. Of the 12 patients, 10 are still living, 16.5 to 55 months after cessation of treatment. The total duration of treatment was two weeks in each case. Two of the patients died of cardiac failure and pulmonary infarction, respectively. Postmortem cultures and microscopic examination of these patients indicated that bacteriologic cure had been effected in each of them. Two patients had relapses within a month after treatment and were successfully treated with a second two week course. It is hoped that this report of a small series of patients will stimulate further investigation of shorter treatment schedules for this disease.

KITCHELL

Kunstadter, R. H., MacLean, H., and Greengard, J.: Mycotic Endocarditis Due to Candida Albicans. J. A. M. A. **149:** 829 (June 28), 1952.

A fatal case of endocarditis and sepsis due to *Candida albicans* in a 7 month old white infant is reported. This is the twenty-fifth case of mycotic endocarditis to be recorded in the literature and the first in an infant. Discussion of the possible explanation for disseminated mycotic infection is presented. From the events in this case and the evidence presented in the literature, it is suggested that the use of antibiotics may be responsible for the enhancement and/or dissemination of mycotic infection.

KITCHELL

BLOOD COAGULATION

Hartmann, R. C., and Conley, C. L.: Studies on the Initiation of Blood Coagulation. III. The Clotting Properties of Canine Platelet-Free Plasma. J. Clin. Investigation **31:** 685 (July), 1952.

It was possible to prepare platelet-free plasma without the use of anticoagulants by means of high-speed centrifugation at low temperature using silicone-treated apparatus. Such platelet-free plasma from normal dogs remained fluid when stored at body temperature in silicone-treated tubes but clotted on contact with glass. The rate of clotting was related to the glass area. When made platelet-free, blood from Irish Setters with a hereditary disease identical with human hemophilia did not clot even when in contact with crushed glass. The authors suggest that the clot-accelerating effect of glass surface is mediated by a "plasma thromboplastin." Hemophilic plasma is presumably deficient in plasma thromboplastin. It appears that either plasma thromboplastin or platelets alone can initiate coagulation, but both components are required for efficient clotting. The clot-accelerating effect of glass surfaces is mediated by the plasma factor rather than by any direct action on platelets.

WAIFE

CONGENITAL ANOMALIES

Fisher, E. R., and Corcoran, A. C.: Congenital Coarctation of the Abdominal Aorta with Resultant Renal Hypertension. Arch. Int. Med. **89:** 943 (June), 1952.

The syndrome of malignant hypertension result-

ing from stenosis of the aortic orifices of the main renal arteries is reported in a 14 year old boy. The stenosis was part of the lesion of coarctation of the abdominal aorta. Associated vascular anomalies indicate that the lesion was congenital.

The findings in this case suggest that antemortem diagnosis of this presently unique condition is possible. Had the condition been recognized, transplantation of the kidney to another, unimpeded arterial circulation might conceivably have been lifesaving. Symptomatically, the attacks of recurrent abdominal pain could be construed as evidences of renal ischemia consequent on transient displacement of these organs; such ischemia was observed in the right kidney at operation. The significance of seemingly complete preservation of intrarenal vessels in the face of severe hypertension as evidence of bilateral renal arterial obstruction is noted. The dilated mesenteric arteries observed in the aortogram and at operation, and ascribed at autopsy to hypertrophy of the left colic artery, are evidence of stenosis and formation of collateral vessels in the mesenteric circulation. Lastly, a careful review of the aortogram after autopsy showed some narrowing of the aorta in the coarcted zone.

BERNSTEIN

Brock, R. C.: Congenital Pulmonary Stenosis. Am. J. Med. **12:** 706 (June), 1952.

The author discusses the classification, incidence, morbid anatomy, clinical manifestations, diagnosis and surgical correction of congenital pulmonary stenosis, which is a congenital narrowing of the tract along which blood flows to the lungs. The narrowing, of various types and at various levels, may occur in the pulmonary artery (pulmonary atresia), at the pulmonary valve (valvular stenosis), in the outflow tract of the right ventricle, the infundibulum (infundibular stenosis), or in the inflow portion of the right ventricle (tricuspid atresia). The fundamental feature in cases of pulmonary valvular stenosis is demonstration and recognition of a diminished blood flow to the lungs which is observed radiologically and by catheterization. Conditions with an increased flow, such as atrial septal defect, transposition of the great vessels, Eisenmenger's complex, interventricular septal defect and primary pulmonary hypertension should be readily excluded. The pulmonary second sound is loud in these conditions in contrast to the normal or quiet sound in pulmonary stenosis. The absence of a systolic thrill and murmur suggests a truncus arteriosus or pulmonary atresia; in these cases a continuous murmur may be heard from a patent ductus arteriosus or from enlarged bronchial arteries. Tricuspid atresia is recognized fairly easily by left preponderance on the electrocardiogram. Recognition of diminished blood flow to the lungs is a strong indication for operation except in those with minimal disability and cyanosis. Operation should be postponed, if possible, until the age of 4 or 5. The best age for operation in the Fallot group is 4 to 14 years. Valvulotomy is advised in all cases of significant pulmonary valvular stenosis. The author concludes with an analysis of 240 cases of congenital pulmonary stenosis he has operated upon. In 82 cases pulmonary valvulotomy was performed.

HARRIS

Froment, R., Gallavardin, L., and Noel, G.: Low Subisthmic Forms of Congenital Stenosis of the Aorta. Arch. mal. coeur **45:** 496 (June), 1952.

The authors report clinical and roentgenologic data on three personal observations of aortic coarctation located peripheral to the common site at the aortic isthmus. The presence of the anomaly was suggested in all three instances by the finding of lower blood pressure in the lower extremities; however, notching of the ribs was absent, and in one case, there was a distinct aortic pulsation palpable in the epigastric region. All three cases were clarified by aortography, which in the first instance showed a stenosis at the level of T9, in the second at L2, and in the third at the level of the diaphragm.

Following an analysis of these three cases and of data in the literature, the authors conclude that an atypical low localization of aortic stenosis should be suspected when one or more of the following atypical findings are present: absence of rib notching; large arterial collateral vessel over the abdominal wall; a systolic murmur heard over the lower thoracic spine; fatiguability of the lower extremities. In every such case aortography is indicated to determine the localization of the stenosis and to prevent surgical intervention at an incorrect level.

PICK

Campbell, M., Gardner, F., and Reynolds, G.: Cor Biloculare. Brit. Heart J. **14:** 317 (July), 1952.

The clinical and radiologic features together with the findings upon catheterization are described of an instance of cor biloculare in a 5 year old child. This anomaly is divided into three types: (1) complete with undivided truncus arteriosus, (2) complete with separate aorta and pulmonary artery, and (3) incomplete with some septal formation but persistent common A-V valve.

The author's case belongs to type two with transposition of the abdominal organs. He suggests that the absence of a sharp border to the "right" ventricle, as seen in the angiocardiograms, may be indicative of a single ventricle.

SOLOFF

Nieveen, J., Homan, B. P. A. A., Marring, W. E., and Van Buchem, F. S. P.: Insertion of the Pulmonary Veins into the Right Atrium. Arch. mal. coeur **45:** 636 (July), 1952.

The authors present case histories of six personal

observations and discuss the diagnosis of anomalous drainage of pulmonary veins into the right atrium. The recognition of this malformation is possible only with the help of cardiac catheterization. The presence of the anomaly is suggested if the oxygen saturation of blood obtained from right ventricular cavities exceeds that of blood from the superior vena cava, or if the saturation of the blood from the latter exceeds that of the blood from the inferior vena cava, and if one succeeds in advancing the catheter into a pulmonary vein. However the latter is also possible if the catheter passes through a septal defect into the left heart and enters normally inserting pulmonary veins from the left atrium. The differential diagnosis between normal and abnormal drainage of these vessels can then be made by following fluoroscopically the pathway of the catheter during its retraction, and by continuous recording of pressure curves. In the case of anomalous insertion, the contour of the pressure curves changes directly to a right atrial contour, while left ventricular or left atrial patterns are interpolated in the presence of a communication of right and left chambers. From the dynamic standpoint anomalous drainage of pulmonary veins becomes important if more than one vessel is involved. This is suggested when typical signs of overload of the right heart are found at examination.

PICK

Smull, N. W., and Lamb, L. E.: Interauricular Septal Defect. Correlation of the Clinical, Radiologic, and Electrocardiographic Findings in Fifteen Cases, with Special Reference Given to the Electrocardiogram. Am. Heart J. **43:** 481 (April), 1952.

The authors present clinical, radiographic and electrocardiographic findings in 15 children in whom the clinical diagnosis of interauricular septal defect was made, proved in one case by autopsy findings. Cardiac catheterizations were not performed. Clinical features included: systolic murmur in all cases, cardiac enlargement in nine cases, congestive failure in four cases, underdevelopment in eight, intermittent cyanosis in five, recurrent upper respiratory infection in a majority. Radiographic findings consisted of prominence of pulmonary arteries in 10, hilar dance in eight, and evidence of right ventricular enlargement in 12. Changes in the electrocardiogram included auricular hypertrophy in two cases, right ventricular hypertrophy in all 15 cases, conduction defects in the form of right bundle branch block in one case and prolonged P-R interval in 10 cases. The authors state that although there is no specific clinical pattern diagnostic for this defect, an accurate clinical diagnosis can be made with proper correlation of the above findings.

HELLERSTEIN

CONGESTIVE HEART FAILURE

Eliekim, M., and De Vries, A.: Observation on the Eosinophil Count in Congestive Heart Failure. Cardiologia **21:** 44 (Fasc. 1), 1952.

The authors report prolonged observations on the number of eosinophils in the blood of patients with congestive heart failure subjected to various types of treatment. The findings were correlated with the clinical condition and changes in body weight, with changes in water, chloride, and sodium diuresis and with the type of therapy.

The administration of mercurial diuretics, digitalis, saltfree diet and other therapeutic procedures caused a rise of the eosinophil count in congestive heart failure, while in control, without evidence of disturbed water and mineral balance, the same treatment resulted in a drop of the eosinophil count. This difference in response is ascribed by the authors to an increase of the blood corticoid level during congestive failure. The fact that a variety of therapeutic agents was equally effective in raising the eosinophil count suggests that the presumed hypercorticoidemia is the result and not the primary cause of congestion.

PICK

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Mathers, J. A. L., and Levy, R. L.: The Prognostic Significance of the Anoxemia Test in Coronary Heart Disease. A Follow-up Study of 254 Subjects. Am. Heart J. **43:** 546 (April), 1952.

In an attempt to appraise the prognostic value of the anoxemia test, the authors made a follow-up study of 254 patients on whom the test was performed during the 10 year period 1937 to 1947. The authors included only cases about whom information could be obtained at least one year after the initial test. It was assumed that subjects not known to be dead as determined by a search of the death certificates of the city of New York were alive at the time the study was terminated. Sixty-three patients died during the follow-up period; in the 16 on whom an autopsy was performed, the clinical diagnosis was confirmed. Analysis of the relationship of the result of the anoxemia test with the clinical status prognosis was inconclusive due, in most instances, to the small numbers involved. In the group with coronary sclerosis and anginal pain, no correlation could be shown between the result of the test and the age of the subject or the duration of symptoms prior to the initial test. Likewise the initial test furnished no information as to the result of a retest 2 or 10 years later, at least for those on whom a retest was made. However, the mortality rate of 45 per cent for the 100 patients with coronary disease and angina was significantly higher than that for the individuals with no cardiovascular disease

during the same period, namely 10 per cent. In the coronary patients with positive tests, the prognosis was worse than those with negative tests. The anoxemia test furnishes an index of the coronary reserve only at the time of its performance, and because of the numerous variables, cannot be used to predict accurately the future clinical course of the patient's coronary heart disease.

HELLERSTEIN

Forssman, O., Hansson, G., and Jensen, C. C.: The Adrenal Function in Coronary Thrombosis. Acta med. scandinav. **142:** 441 (Fasc. VI), 1952.

Many observations made in the past point to increased adrenocortical function as the cause of the initial hyperglycemia observed in many instances of acute coronary thrombosis. These workers used several technics for studying adrenocortical function in patients with acute myocardial infarction. A significant eosinopenia was found in practically all cases, decreasing each day and usually becoming normal by the eighth day. The degree of eosinopenia correlated well with the elevation of temperature, less well with the degree of leukocytosis and least well with the blood sugar values. An initial pathologic rise in the excretion of 11-oxysteroids occurred in 18 out of 34 cases and an increase in excretion of 17-ketosteroids was recorded in 25 out of 60 cases. Increases in steroid excretion occurred particularly in those patients with marked shock, fever, eosinopenia to more than 10 per cent of normal leukocytosis and hyperglycemia. A rise in the urinary excretion of catechols (adrenaline, noradrenaline, or both) was observed in 14 of the 15 patients in whom the studies were made. Considerable variation in the pattern of steroid excretion was observed from case to case.

Wang, I.: Cholesterol Tolerance in Coronary Thrombosis. Brit. Med. J. **4771:** 1278 (June), 1952.

The author describes his method of doing a cholesterol-tolerance test. The results showed that there was no abnormal postabsorptive increase in blood cholesterol in coronary thrombosis. The results of this cholesterol-tolerance test suggested that there might be intolerance of ingested cholesterol in a small group of patients, those with nephritis, diabetes mellitus and myxedema.

BERNSTEIN

Brigden, W., and Shillingford, J.: The Vectorcardiogram of Cardiac Infarction. Brit. Heart J. **14:** 339 (July), 1952.

The authors used their simple method of drawing the spatial vectorcardiogram of 20 instances of myocardial infarction and then reconstructed the conventional leads. There was a close resemblance between the reconstructed leads and the leads obtained by conventional electrocardiography. The cardiac vectors tend to point away from the infarction.

This method adds nothing to the diagnosis of infarction, but the authors believe that the vectorcardiogram provides a more unified picture of the abnormal electrical activity of the heart as a whole.

SOLOFF

Plotz, M.: Sedimentation Rate in Myocardial Infarction. Am. J. M. Sc. **224:** 23 (July), 1952.

Using the Wintrobe method with hematocrit correction, the author examined the sedimentation rates encountered in 100 consecutive cases of myocardial infarction. The diagnosis was based on definite electrocardiographic changes or autopsy findings. A rapid sedimentation rate, greater than 18 mm. per hour, was noted in 97 per cent of the patients; the range of values lay between 18 and 56. The maximum rate of fall occurred between the third and seventh day with a gradual return beginning by the eighth day. In most cases the sedimentation rate had returned to normal by the thirty-sixth day. There appeared to be no correlation between the sedimentation rate and the severity of the illness or the ultimate prognosis. In 21 patients the sedimentation rate remained elevated; three had fresh infarctions, three were found to have unsuspected malignancies, six were found to have pulmonary infection, there were three with phlebothrombosis, one had rheumatoid arthritis, and in five patients no cause could be found for the persistence of the rapid rate. It is felt that the sedimentation rate is a satisfactory diagnostic aid in myocardial infarction, especially in cases without much temperature elevation.

SHUMAN

Bengtson, E., and Pejme, J.: Acute Cardiac Infarction Associated with Serum Sickness. Cardiologia **21:** 58 (Fasc. 1), 1952.

Eight days following an injection of antitetanic serum, a 21 year old man with previously normal heart developed typical clinical signs of serum sickness and, at the same time, pronounced precordial pain with drop of blood pressure, leukocytosis and elevation of the sedimentation rate. The electrocardiogram showed a classic pattern of recent anterolateral wall infarction followed by a typical evolution. Subsequently the patient developed signs of heart failure, and anginal pain persisted over a six month period of observation. Negative bacteriologic cultures from the pharynx and normal anti-streptolysin and staphylolysin titers in the blood ruled out the possibility of a myocarditis. The development of cardiac findings coincident with the onset of the serum sickness suggested very strongly that in this instance myocardial infarction was the result of an allergic cardiovascular reaction.

PICK

ELECTROCARDIOGRAPHY

Scherf, D., and Dix, J. H.: The Effects of Posture on A-V Conduction. Am. Heart J. **43:** 494 (April), 1952.

The authors studied the effect of a change from the recumbent to the upright position in 31 patients with A-V conduction disturbances. In 26 of 30 cases with partial A-V block, shortening of the P-R interval occurred, without a change of rate, and often appeared after a latent period of 10 to 15 seconds. When the patients resumed the recumbent position, the P-R interval again became prolonged, although not immediately to its former value. In three of the four patients with no shortening of the prolonged P-R intervals on standing, bundle branch block existed. No change occurred in one case of complete A-V block.

The modifications of A-V conduction produced by standing cannot be ascribed solely to changes in tonus of the autonomic nerves, that is, increase of sympathetic tonus and a reciprocal decrease of the vagus tonus. In many cases the increase of rate and shortening of the A-V conduction were independent of each other. The authors discuss the complex nature of the influences on A-V conduction and suggest that other, as yet unknown, factors may play a role.

HELLERSTEIN

Gross, D.: A Single Numerical Correlation Between the Quotient Q-T/T-Q and Cardiac Rate in Healthy Adults. Am. J. Physiol. **170:** 121 (July), 1952.

The quotient (Q-T)/(T-Q) represents the ratio of systole to diastole within the cardiac cycle. This ratio is correlated with heart rate according to the formula: (Q-T)/(T-Q) = rate/100. This quotient is unchanged with reference to rate in the recovery period after exercise. During expiratory effort it is changed, however. Values measured are greater than predicted.

OPPENHEIMER

Eliaser, M., Jr., and Giansiracusa, F.: The Electrocardiographic Diagnosis of Acute Cor Pulmonale. Am. Heart J. **43:** 533 (April), 1952.

The authors present electrocardiographic changes in eight patients with acute pulmonary embolism or pulmonary infarction. Electrocardiographic findings of acute cor pulmonale consisted of the following: shift of the transitional zone to the left, eight cases; cardiac rotation clockwise and vertically, six cases; right ventricular strain (inversion of T waves in V_1 to V_4) four cases; ST-T changes of coronary insufficiency, four cases; auricular arrhythmias (auricular fibrillation or premature beats), three cases; pulmonale P waves, two cases; and transient right bundle branch block, one case. The speed with which the associated electrocardiographic changes appear is a diagnostic feature that frequently aids in differentiating acute cor pulmonale from myocardial infarction. Coronary insufficiency (depression of the S-T segments in left precordial leads) combined with rotational changes of the heart associated with right ventricular dilatation accounted for the "staircase" ascent of standard leads I and II. In none of the patients was the presence of posterior myocardial infarction a confusing factor. In four patients a Q-wave was present in leads III and/or aV_F, occurring as a manifestation of the rotational changes in acute cor pulmonale. The authors emphasize the importance of serial records to detect minor shifts of the transitional zone and electrical axis.

HELLERSTEIN

Berthoud, E., and Goldschlag, H.: The Electrocardiogram in Chronic Alcoholism. Cardiologia **20:** 367 (Fasc. 6), 1952.

Electrocardiograms of 224 chronic alcoholics were analyzed with regard to the presence of abnormalities. In 86.5 per cent the findings were within normal limits; 5.5 per cent were border-line tracings, and in 16 cases (8 per cent) there were definite abnormalities which could not be accounted for by associated cardiovascular disease.

The most frequent anomaly was flattening of the T wave in the limb leads and/or left precordial leads: this was present in 11 of the 16 cases classified as abnormal. Occasional findings were auricular fibrillation, bundle branch block, abnormalities in the size of QRS deflections and deviations of the S-T segment.

While these results of the investigation confirm the occurrence of electrocardiographic alterations which can be attributed to chronic alcoholism, their incidence appears to be much lower than described by others.

PICK

Gillman, H.: Differentiation of Forces Determining the Appearance of Precordial Leads. Cardiologia **20:** 314 (Fasc. 6), 1952.

There is much disagreement whether unipolar precordial can be considered to be projections of the integrated cardiac vector upon the horizontal (coronal) plane. The validity of such a concept has been questioned mainly with regard to the influence of proximity potentials and of the conductivity of tissues surrounding the heart, which varies according to the different positions of the electrode over the precordium.

In order to test the validity of these objections the author compared the size of deflections of actual precordial leads with calculated values (a) of projections of the horizontal vectorcardiogram (obtained by the method of Duchosal and Sulzer), and (b) of projections corrected according to the distance of the chest position from the assumed

center of the heart. Curves constructed from these three types of data were very similar except in cases with large pleural effusion or with pneumothorax.

The author concludes that, under normal conditions, the projection of the integrated cardiac vector upon the horizontal plane is the principal factor which determines the contour of the precordial electrocardiogram. While proximity potentials appear to be of only minor importance variations of tissue conductivity and unpredictable deviations of the potential lines in the thorax may account for some disagreement between actual and constructed precordial patterns.

PICK

Ferrero, C., and Baezner, C.: Evolution of Electrocardiographic Tracings Indicating Left Ventricular Strain. Cardiologia **20:** 371 (Fasc. 6), 1952.

Among 126 cases with chronic heart failure, 108 of which had hypertensive and/or arteriosclerotic heart disease, the authors found 103 instances with the electrocardiographic pattern of left heart strain. This material was arbitrarily divided into three groups according to the degree of the electrocardiographic anomaly.

The mortality within a period of two and a half years was 25 per cent among cases without abnormalities in the electrocardiogram, and twice as high among cases with the left heart strain pattern. However, the type of evolution of the electrocardiographic anomaly was very variable and no correlation could be established as to the degree of the anomaly and prognosis. The incidence of death also appeared unrelated to the age of the patient at the beginning of the disease, to the duration of its clinical evolution and to ophthalmologic alterations. On the other hand, the presence of arterial hypertension, clinical evidence of left ventricular hypertrophy and certain disturbances of the cardiac rhythm definitely tended to aggravate the mortality risk of the patients.

PICK

Brandt, J. L., Caccese, A., and Dock, W.: Slit-Kymographic Evidence that Nitroglycerine Decreases Heart Volume and Stroke Volume While Increasing the Amplitude of Ballistocardiographic Waves. Am. J. Med. **12:** 650 (June), 1952.

Nitroglycerine given in doses which accelerate the pulse decreases stroke volume and heart volume. The effect on minute volume is variable, but the increase is never large. The systolic waves of the ballistocardiogram usually increase in amplitude after nitroglycerine and appear related to the increased velocity of ejection rather than to the volume ejected. Resistance to systolic ejection is actually decreased by nitroglycerine and the speed of initial ejection is high. As a result I-J amplitude rises even when stroke volume is decreased. An increased depth of the K wave was a striking feature in most of the postnitroglycerine curves. This suggests vasodilatation in the splanchnic area or a sharper peak on the wave of flow down the aorta.

The authors conclude that the ballistocardiograph yields misleading data when stroke volume is calculated during action of drugs or diseases which alter duration or force of systole, or the arterial resistance or venous return. The clinical value of the ballistocardiograph lies in its sensitivity to velocity of systolic ejection, which no other method of study duplicates, and not in estimating stroke volume. The slitkymograph may be more useful in estimating the changes in heart volume and in stroke volume occurring under drug action than in absolute measurements of either volume or stroke.

HARRIS

Landman, M. E., and Ehrenfeld, I.: Ventricular Fibrillation Following Eyeball Pressure in a Case of Paroxysmal Supraventricular Tachycardia. Am. Heart J. **43:** 791 (May), 1952.

The authors present a case report of a 46 year old woman with recurrent supraventricular tachycardia which was terminated by eyeball pressure. A short run of six bizarre ventricular complexes developed prior to conversion to normal sinus rhythm. Within the next 15 seconds there were two runs of four, and one of two ventricular beats. The outcome was not fatal. In view of the bizarre and varied character of the individual complexes and the fact that one followed another without pause it was the opinion of the authors that these runs represented true ventricular fibrillation, rather than multifocal polymorphic ventricular premature contractions. The potential danger of vagal stimulation of the heart includes the possibility of complete cardiac arrest and the hitherto unconsidered danger of ventricular fibrillation.

HELLERSTEIN

Hay, J. D., and Keidan, S. E.: Persistent Ectopic Auricular Tachycardia in Children. Brit. Heart J. **14:** 345 (July), 1952.

The authors describe rapid auricular arrhythmias in three children which persisted for prolonged periods. In one, there was no evidence of the existence of normal conduction. Failure may not occur if the heart is otherwise normal.

SOLOFF

Cookson, H.: Paroxysmal Ventricular Standstill. Brit. Heart J. **14:** 350 (July), 1952.

The author describes three instances of paroxysmal ventricular standstill as an episode during normal sinus rhythm. These attacks occurred over a period of years.

He stresses the difficulty, in the absence of electrocardiographic proof, of differentiating these attacks from epilepsy.

He believes the attacks may be precipitated by reflexes from the carotid sinus, pharynx or esophagus or by emotional disturbances.

SOLOFF

ENDOCRINE EFFECTS ON CIRCULATION

Schmidt, S.: Pericardial Effusion in Myxoedema. Brit. J. Radiology **25:** 389 (July), 1952.

A case of "myxedema heart" with verified pericardial effusion is presented. The effusion which remained after aspiration resorbed under thyroid treatment and did not reappear. The hearts of several untreated myxedema patients other than the one reported above were examined, but none of them showed evidence of pericardial effusion. The radiologic diagnostic criteria of pericardial effusion in myxedema are presented.

BERNSTEIN

HYPERTENSION

Smirk, F. H., and Chapman, O. W.: Comparison of the Effects of Veratrum Alkaloids and of Hexamethonium Bromide upon the Blood Pressures in Arterial Hypertension. Am. Heart J. **43:** 586 (April), 1952.

The authors summarize their experience with veratrum alkaloids and hexamethonium bromide in the treatment of 36 and 27 patients, respectively, with arterial hypertension. The minimum effective dose of Anatensol was from 1 to 3 mg., and between 20 and 50 Craw units of Vertavis. Hexamethonium bromide was administered orally with an initial dose of 125 mg., on an empty stomach and at six hour intervals. The initial subcutaneous dose was 15 mg. at five hour intervals. Substantial reduction of blood pressure was possible in only 10 of 36 patients with the mixed veratrum alkaloids, and in all of 27 patients with hexamethonium bromide injected subcutaneously. The latter treatment was maintained for periods of one to 15 months, with no deaths due to the drug action. The therapeutic range of dosage of both groups of drugs is narrow, although hexamethonium was considered easier to regulate. The main advantages of hexamethonium bromide are its reliability of action and easy correction of side effects due to excessive fall in blood pressure by lying flat. The major disadvantage is the need for frequent daily subcutaneous injections. The disadvantages of veratrum alkaloids consist of the poor response (only one-third to one-quarter had blood pressure reductions of 40 to 80 mm. of mercury without severe toxic effects), and distressing toxic effects (vomiting, retching, choking sensations, and bradycardia). After veratrum alkaloids, postural hypotension is inconspicuous and little or no toleration develops, unlike the effects of hexamethonium bromide. The authors consider hexamethonium bromide administered subcutaneously as the most widely applicable agent so far available for the effective reduction of high blood pressure.

HELLERSTEIN

Kahn, J. R., Skeggs, L. T., Shumway, N. P., and Wisenbaugh, P. E.: The Assay of Hypertensin from the Arterial Blood of Normotensive and Hypertensive Human Beings. J. Exper. Med. **95:** 523 (June), 1952.

A direct method for the isolation and assay of hypertensin from blood was therefore developed. This study is concerned with the application of this method to the isolation and assay of hypertensin in the blood of human beings with normal blood pressures and those with benign and malignant hypertension. The concentrations of hypertensin in the blood of patients with the malignant phase of essential hypertension were found to be greatly increased. The concentrations of hypertensin found in patients with benign hypertension had a moderate degree of overlapping with those found in the normotensive group, but the mean concentration of hypertensin in the former group was twice that of the controls.

BERNSTEIN

Montagu, J. D.: Use of Hexamethonium Bromide and Decamethonium Iodide with Electroplexy. Brit. M. J. **4772:** 1336 (June), 1952.

The patient herein reported suffered from a psychiatric illness accompanied by severe hypertension. The former was successfully treated by means of electric convulsion therapy in conjunction with a muscle relaxant, decamethonium iodide (C10), and a depressor substance, hexamethonium bromide (C6). The technic was highly successful. This patient's convulsions were fully suppressed, although he received 0.5 mg. per 6.4 Kg. of body weight. It is suggested that a single intramuscular injection of C6 might profitably be given before each shock in cases with severe hypertension, if electric convulsive treatment is indicated on psychiatric grounds but contraindicated by the physical condition.

BERNSTEIN

McQueen, E. G.: Hexamethonium Bromide and Kidney Function. M. J. Australia. **769:** 1 (June), 1952.

The sole method of removal of hexamethonium bromide is by excretion via the kidneys. Renal excretion is almost solely by filtration. In patients with good renal function even a considerable fall in blood pressure is accompanied by no more than a transient fall in glomerular filtration rate and renal plasma flow. The rapidity with which these are restored indicates that renal hemodynamic readjustments take place to compensate for the fall in blood pressure. The most likely mechanism is abolition of tone in glomerular arterioles by the C6. Even in the presence of fairly severe impairment of renal

function, a moderate fall in blood pressure will not produce a dangerous fall in glomerular filtration rate. However, a gross fall may be dangerous. Experiment suggests that patients with severe arteriosclerosis are least able to compensate for a gross fall in blood pressure. The disproportionate fall in urine flow must be mainly tubular in origin and must result from increased reabsorption of salt and water. It is not apparently mediated by endocrine mechanisms.

BERNSTEIN

Rosenfeld, S.: Production of Persistent Hypertension Induced in the Rabbit by Occlusion of the Arteries Supplying the Brain. Am. J. Physiol. **169:** 733 (June), 1952.

Persistent hypertension, with a tendency to rise, remains for as long as eight months after limiting blood flow to the brain of rabbits. In these experiments the carotid sinus does not appear to be a factor in the production of this hypertension. When the carotid sinuses are excised in rabbits the ensuing hypertension is not entirely due to the buffer nerve mechanism. It is pointed out that the results may be due entirely to interference with cerebral blood flow.

OPPENHEIMER

Gropper, A. L., Cockrell, E. W., Raisz, L. G., and Pulaski, E. J.: Comparison of Dextran and Oxypolygelatin in Treatment of Hemorrhagic Hypertension. Am. J. Physiol. **169:** 749 (June), 1952.

In standardized hemorrhagic hypotension 22 per cent dextran-treated dogs died as compared with 33 per cent for oxypolygelatin and 85 per cent for untreated controls. With both these agents blood pressure rises more rapidly and to higher levels than with saline. Dextran expands blood volume more and for a longer time than oxypolygelatin or dog plasma. Dextran is better than oxypolygelatin for restoration of glomerular filtration and renal plasma flow. Dextran draws about twice as much fluid from interstitial spaces as does oxypolygelatin. Postmortems were negative for both substances.

OPPENHEIMER

PATHOLOGY

King, E. S. J.: The Haemodynamics of Subintimal Hemorrhage. Australasian Ann. Med. I:18 (May), 1952.

The conditions necessary for hemorrhage to occur in the intima of an artery will be found only when there is already alteration in the size of the lumen and obstruction to the flow of the blood. Development of subintimal hemorrhage and associated thrombosis is not the exciting factor in the occlusion and myocardial infarction since it has been shown that there is frequent lack of correlation between the age of the subintimal hemorrhage or thrombus and that of the infarct. It is therefore necessary to look elsewhere in the physiology of the circulation for the explanation of myocardial infarction in these cases. It is certainly not due to vascular obstruction from subintimal hemorrhages of coronary vessels.

BERNSTEIN

Sladden, R. A.: Coronary Arteriosclerosis and Calcification in Infancy. J. Clin. Path. **5:** 175 (May), 1952.

It appears to be generally agreed that no single etiologic factor has been identified as the cause of coronary ateriosclerosis and calcification in infancy. There is evidence in some cases that renal disease may play an important role; arterial calcification is known to have occurred in some cases of renal rickets in older children. In a majority of cases no satisfactory etiology has been found. Other reputed etiologic factors include syphilis, other infections, allergy, and hypervitaminosis D. The authors report two cases in which no etiologic factor could be found. The disease has been reported in a still born infant. There are 19 males, 12 females, and two cases of unstated sex in a total of 33 cases, including the two cases reported here. There have been no constant findings of apparent significance in the histories of pregnancy, delivery, or upbringing. Once the child becomes ill there is usually a fairly steady downhill course terminating in death in a few days or weeks.

The essential pathologic lesion is found in the medium-sized arteries of the body, including the coronary arteries, and consists of fibroblastic proliferation of the intima with calcification occurring in close relationship to the internal elastic lamina and spreading into the medial coat and proliferated intima. There are varying degrees of disorganization of the vessels, obstruction of the lumina and recanalization, round cell, and occasional giant cell or eosinophilic infiltration of the vessel walls. These changes have been reported from nearly all parts of the body, including the brain, lungs, abdominal viscera, and limbs. The aorta may also show some calcification in relation to the elastic fibers of the media. If coronary occlusion occurs, myocardial necrosis and calcification of the affected muscle may take place. The left ventricle and papillary muscles are frequently involved.

BERNSTEIN

French, J. E.: A Histological Study of the Heart Lesions in Potassium-deficient Rats. Arch. Path. **53:** 485 (June), 1952.

The author produced the myocardial degeneration of potassium deficiency in rats which were protein-depleted and then given repletion diets deficient in potassium to produce a cardiac lesion similar to that caused solely by potassium deficiency but more extensive and more quickly produced. The induced lesion can result in myocardial failure. Control

groups of protein depleted and repleted rats were treated with ample potassium in contrast with deficient potassium. The characteristic myocardial changes in rats ranged from loss of striation, swelling and homogenous staining with the red component of the trichrome stain to complete disintegration. In some areas sarcoplasm was largely lost, with only the nuclei remaining as "myogenous" cells. There was an interstitial infiltration of edema, polyblasts, macrophages and fibroblasts.

The addition of potassium to the diet in such animals quickly stopped any further development of the lesion. The interstitial changes cleared and the myocardial fiber pathology disappeared within two or three days. The author emphasizes that the lesion is not specific for potassium deficiency and that it cannot be explained simply by potassium deficiency because many complex biochemical processes may be associated with it.

GOULEY

Bierman, H. R., Perkins, E. K., and Ortega, P.: Pericarditis in Patients with Leukemia. Am. Heart J. **43:** 413 (March), 1952.

The authors present four cases of leukemia (two lymphogenous, two myelogenous) in which pericarditis appeared as a serious complication and contributed toward death in three of these patients. The clinical picture was characterized by increasing dyspnea, decreased pulse pressure, tachycardia, friction rub, enlarged cardiac shadow, S-T elevation, low voltage and flat to inverted T-waves. At postmortem examination organizing fibrinohemorrhagic pericarditis with effusion, leukemic infiltration of the pericardium and adhesions were found. The author states that the sudden appearance of cardiac symptoms in the absence of previous cardiac disease in a leukemic patient should arouse the suspicion of infiltration of the heart or pericardium. If this complication is recognized early, symptomatic relief can be afforded, for a time at least, by routine cardiac therapy.

HELLERSTEIN

Seaman, A. J., and Christerson, J. W.: Demonstration of Lupus Erythematus Cells in Pericardial Fluid. J. A. M. A. **149:** 145 (May 10), 1952.

Lupus erythematosus cells were demonstrated in buffy coat preparations of oxalated pericardial fluid aspirated from a white woman (38 years old) with pericardial effusion, splenomegaly, perisplenitis, and hepatomegaly. Remission was induced by cortisone therapy and the case is presented to emphasize the fact that Wright stain preparations of pericardial fluid may alert one to the possibility of disseminated lupus erythematosus as the underlying disease in some cases of pericarditis.

KITCHELL

PHARMACOLOGY

Smythe, C. M., Nickel, J. F., and Bradley, S. E.: The Effect of Epinephrine (USP) l-Epinephrine, and l-Norepinephrine on Glomerular Filtration Rate, Renal Plasma Flow, and the Urinary Excretion of Sodium, Potassium, and Water in Normal Man. J. Clin. Investigation **31:** 499 (May), 1952.

The authors studied the effects of purified products from the adrenal medulla on renal hemodynamics and water electrolyte excretion in normal subjects. The urinary excretion of sodium and potassium was depressed by epinephrine, l-epinephrine, and l-norepinephrine. Over-all vasodilatation was manifest in elevated cardiac output with little or no change in mean arterial pressure during the action of l-epinephrine and epinephrine (USP), although generalized vasoconstriction as evidenced by diminished cardic output and elevated pressure was found during response to l-norepinephrine. Additional evidence strongly suggests augmented tubular reabsorption of sodium and potassium; furthermore, there was a suggestion that these drugs interfere with the tubular reabsorption of water, since urine flow increased somewhat during the action of these hormones and fell off sharply on withdrawal. Epinephrine (USP), a mixture of the two, behaves in general like l-epinephrine in its action on the circulation of the kidney.

WAIFE

Keet, J. E., Halsted, G. O., Collins, V. J., and Rousselot, L. H.: Intra-Arterial Infusion—Simplified Technique. J. A. M. A. **149:** 418 (May 31), 1952.

A relatively simple apparatus has been assembled by the authors for intra-arterial infusion. This consists of an ordinary blood bottle of the Baxter or Cutter type, a hand bulb from a sphygmomanometer connected through a "Y" metal adapter to the air inlet of the blood bottle and to a manometer. A plastic cylinder containing a small cotton plug is incorporated to insure sterility as an air filter. The arterial cannula consists of a specially modified 15 gage spinal needle for adults or an 18 gage for children. Eighteen intra-arterial infusions have been performed without complication. The authors discuss the role of vasospasm in the production of gangrene following intra-arterial transfusion, and they use simple pressure after the arterial puncture to prevent bleeding. It is hoped that simplification of apparatus and technic will make for more widespread use of this valuable therapeutic measure.

KITCHELL

Pullman, T. N., and McClure, W. W.: The Effect of L-Nor-Adrenaline on Electrolyte Excretion in Normal Man. J. Lab. & Clin. Med. **39:** 711 (May), 1952.

The present study was undertaken to determine

he effect of clinically pure l-noradrenaline on odium, chloride and potassium excretion in man, nd to gain insight into the mechanisms by which uch changes might occur.

No apparent change was noted in the sodium nd chloride clearances of six human subjects. The argest change was observed in the clearance of otassium, which fell sharply when the l-noradrena- ine infusion was used. The depression of the potas- ium clearance seemed to parallel the depression of enal plasma flow more closely than it did the in- rease in dose of l-noradrenaline.

These findings are compatible with, but are not roof of, the hypothesis that reduction in renal lasma flow, by reducing the total tubular load of otassium diminishes the tubular secretory rate of otassium.

MINTZ

Laszt, L., and Kreuzer, F.: Comparative Experiments on Circulatory Effects of Adrenaline and Arterenol. Arch. Kreislaufforsch. **18:** 176 (May), 1952.

The authors studied the effects of epinephrine and norepinephrine upon the cardiovascular dynamics in anesthetized dogs with open chests. Pressures in the left ventricle and in peripheral vessels were determined by direct cannulation and the total peripheral resistance calculated according to the formulas of Broemser and Ranke.

Contrary to most of the previous reports, a similar elevation of blood pressure could be demonstrated following intravenous injection of equivalent doses of both preparations as long as the initial pressure remained normal. With falling initial pressure, the effect of epinephrine became progressively weaker and finally disappeared completely, while the action of norepinephrine was somewhat delayed but quantitatively unchanged. Both substances produced tachycardia and an increase of the total peripheral resistance, the latter effect being more marked following norepinephrine.

PICK

Ludwig, H.: Comparative Treatment with Digitalis. Arch. Kreislaufforsch. **18:** 118 (May), 1952.

There are three methods for evaluation of the potency of a digitalis preparation in clinical cases. The substance may be used in large group of unselected patients and its effect roughly compared with the effect of other known preparations. In the second method, two small and equal groups of patients may be carefully selected according to certain sign and symptoms, one being treated with the unknown preparation, the other with a drug of known potency, and the results then compared. A third method consists in using different preparations successively on a single patient whose response to digitalis is known.

The author used all three methods for evaluation of various well known commercial digitalis preparations and came to the following conclusions: Digitoxin is not suitable for rapid initial digitalization because of its rapid absorption and tendency to cumulation resulting frequently in early signs of toxicity. It can, however, be best recommended for maintenance of compensation achieved by other preparations. Oral K-strophanthin, although acting rapidly, is difficult to handle since its rate of absorption varies greatly in various individuals and, hence, it is very difficult to establish an appropriate dosage. Digoxin and Cedilanid have about the same rapid effect on intravenous application; however, on oral application digoxin acts about three times faster. The latter is, therefore, recommended for cases in whom rapid oral digitalization is intended, while Cedilanid should be reserved for intravenous use.

PICK

Gross, F., and Schneider, J.: Further Investigations on Circulatory Changes Following Injection of Adrenaline and Noradrenaline into the Spleen. Helvet. Physiol. et Pharmacol. Acta **10:** 207 (May), 1952.

Injection of a small amount of epinephrine into the splenic artery in cats and dogs is followed by an increase of blood pressure, which is more pronounced than that seen following injection of the same amount into the splenic or a peripheral vein. Tachycardia following intravenous injection is modified to bradycardia upon intrasplenic injection. Norepinephrine has the same effects upon intrasplenic injection. The blood pressure rise and the reaction of the heart resemble those seen following electrical stimulation of splenic nerves; they can be augmented by ganglionic blocking substances (Pendiomide) and prevented by sympathicolytic drugs (Regitine). The stimulation of a splenic nerve following intrasplenic injection of epinephrine does not provoke an additional increase of blood pressure and frequently results in decrease of the latter. However, augmentation of pressure is seen if the injection is made following stimulation of the nerve. The authors conclude that intrasplenic injection of epinephrine liberates a substance which acts upon the circulation in a similar manner as norepinephrine.

PICK

Kleiber, E. E.: Parenteral Administration of Ammivin (Khellin) in the Treatment of Coronary Disease. Ann. Int. Med. **36:** 1179 (May), 1952.

Intramuscular Ammivin, a purified aqueous suspension of the active constituent of Ammi Visnaga in isotonic sodium chloride, containing 50 mg. of khellin per cubic centimeter, was used in the treatment of 16 ambulatory private patients with coronary disease characterized by either typical effort angina, angina decubitus, or chronic coronary insufficiency, and of two patients who proved to

have chest pains due to extracardiac causes. Dosage levels were determined by trial and error. The majority, however, after an initial dose of 1 cc. intramuscularly were given 2 cc. once a week over a period of many months. Gastrointestinal disturbances with this dosage were entirely absent, but where the frequency of the injection was increased to every two to three days, nausea and vomiting often appeared. Excellent results were noted in one-third of the cases with genuine angina as judged by the lessening in severity and frequency of the anginal episodes and reduction in need for nitroglycerine. All other patients with the exception of those unable to tolerate the drug or having pains due to extracardiac causes, were at least moderately improved. Some patients had not had the drug for sufficient time truly to evaluate it, though the immediate effect is promising. Acute coronary insufficiency as evidenced by angina decubitus appeared to be more quickly controlled and eradicated with injectable Ammivin than with any other of the usual measures employed for the treatment of this disorder. The data resulting from this study seemed to indicate that injectable khellin is superior to oral preparations of the drug because, with the former, there is a higher incidence of improvement of symptoms and a lower proportion of troublesome gastrointestinal symptoms.

WENDKOS

Swan, H. J. C.: Noradrenaline, Adrenaline, and the Human Circulation. Brit. M. J. **4766:** 1003 (May), 1952.

Noradrenaline, the transmitter substance of the sympathetic nerves, has a predominantly local action and its steady release at the nerve endings causes constriction of the local blood vessels. The over-all activity of the sympathetic nerves results in the normal peripheral vasomotor resistance, which is a major factor in the maintenance of the blood pressure.

Adrenaline is an "emergency substance" liberated into the circulation and acting generally. Under physiologic conditions it causes an over-all vasodilatation and an increase in cardiac output. Noradrenaline would appear to be the most rational agent in the treatment of the hypotensive state due to peripheral collapse.

BERNSTEIN

Krayer, O.: Antiaccelerator Cardiac Agents. J. Mt. Sinai Hosp. **19:** 53 (May–June), 1952.

The veratrum alkaloids of steroid nature, veratramine, veratrosine, jervine, and pseudojervine, all secondary amines, were found to have a selective blocking action on the cardio-accelerator mechanism of the mammalian heart. The tertiary veratrum alkamines or their esters did not possess this pharmacologic action. Using a continuous infusion of epinephrine or norepinephrine to produce a steady level of acceleration of the cardiac rate in the dog's heart–lung preparation, it was demonstrated that adequate doses of the secondary amines could restore the heart rate to normal despite the continued infusion of the sympathomimetic amine, an effect not abolished by atropine but overcome by larger doses of epinephrine. The accelerator effect of ephedrine could likewise be inhibited. These compounds could also antagonize the heart rate increase in the "spinal cat" with an acutely denervated heart caused by stimulation of the postganglionic nerve from the stellate ganglion. These changes in heart rate appear to be due to a decrease in the sensitivity of the pacemaker tissue to the accelerator effects of the sympathomimetic amines, an effect which the author designated as an "antiaccelerator action." It was found that heat still caused an increased heart rate in the presence of veratramine. Further studies showed that veratramine could prevent cardiac acceleration by epinephrine without preventing the influence of epinephrine upon the force of contraction leading to an increase in the work capacity of the heart. These compounds were incapable of abolishing the vasopressor effect of a continuous infusion of epinephrine or norepinephrine in the spinal animal, nor the inhibitory effect of epinephrine on the isolated small intestine of the rabbit, but they did antagonize the motor effect of epinephrine and stimulation of the sympathetic nerve on the nictitating membrane of the cat.

The chemistry of these secondary amines was discussed, with the importance of the piperidine ring to activity being demonstrated. The toxic action of these compounds prohibit their use in man, but they remain an interesting pharmacologic tool in view of their high degree of selectivity of action.

CORTELL

Handelsman, M. B., Levitt, L. M., and Conrad, H. Jr.: Small Vessel Dysfunction in Patients with Diabetes Mellitus: I. Skin Temperature Response to Priscoline in the Toes of Diabetics. Am. J. M. Sci. **224:** 34 (July), 1952.

In normal subjects, the injection of Priscoline produces an over-all increase in the blood flow to the limbs, an increase in skin temperature, and a probable decrease in muscle blood flow. In this study two groups of patients, diabetics with no evidence of arterial insufficiency and normal subjects, received 50 mg. of Priscoline intravenously while skin temperature readings were obtained at five-minute intervals thereafter. The results demonstrated that 40 per cent of the diabetic patients had an inadequate response in skin temperature to the vasodilator. This indicates that dysfunction of the small vessels can exist independently of the state of the larger vessels.

SHUMAN

Feinblatt, T. M., and Ferguson, E. A.: Protection of Cardiac Glycosides from Action of Light by Actinic Desensitizer (Red Dye). New England J. Med. **246:** 905 (June), 1952.

Digitalis in solution has a limited shelf-life primarily because of absorption of actinic rays. This is true particularly of green solutions. These workers found that a stabilized tincture of digitalis may be prepared and dispensed in clear-glass bottles by removing all green coloring matter by contact procedures with animal charcoal and the subsequent addition of aniline red or phenylsafranine. Comparison of specially decolorized solutions to which 0.1 per cent phenylsafranine or 0.1 per cent amaranth red had been added with standard tincture of digitalis, U. S. P. XII, disclosed that the former had twice the shelf-life of the latter. It mattered little if the special solutions were stored in brown or clear-glass bottles. When kept in clear-glass bottles or under unusual conditions of light or heat standard tincture of digitalis may deteriorate to a level below U. S. P. requirement within only three to six months.

ROSENBAUM

Baylis, J. H., and Kauntze, R.: The Effect of Dimercaprol on Hypertension. Lancet **6718:** 1092 (May), 1952.

The author injected dimercaprol intramuscularly in doses of 3 to 6 mg. per kilogram of body weight into four patients with essential hypertension. The blood pressure rose slightly or moderately with 3 to 4 mg. per kilogram of body weight and alarmingly with 6 mg. per kilogram. The rise in blood pressure usually began 20 to 30 minutes after injection and persisted for 50 to 100 minutes. With intramuscular dimercaprol 6 mg. per kilogram of body weight the rise in blood pressure was more extensive (from 225/145 to 265/185 mm. Hg), of shorter duration, and accompanied by increase of heart rate.

BERNSTEIN

Furman, R. H., and Geiger, A. J.: Use of Cholinergic Drugs in Paroxysmal Supraventricular Tachycardia. J. A. M. A. **149:** 269 (May 17), 1952.

In this report the hazards of the conjoint use of Neostigmine and methacholine chloride in the treatment of paroxysmal supraventricular tachycardia are discussed with three case reports. In two of the cases treatment was successful but not without danger; and in the third, death followed a second injection of methacholine chloride given 40 minutes after a dose of Neostigmine. It was assumed that death was due to the potentiation of the effects of the methacholine chloride by the previously administered Neostigmine. Suggestion is made that methacholine chloride should not be injected sooner than four hours after an injection of Neostigmine. Suggestions are also made for more adequate technical preparations for the emergency administration of pharmacologic antidotes directly into the circulation if alarming reactions develop after administration of such drugs.

KITCHELL

PHYSIOLOGY

Kowalski, H. J., and Rutstein, D. D.: The Distribution of the Thiosulfate Ion with Respect to Normal Human Serum and Red Blood Cells and its Application to "Extracellular Fluid" Determination. J. Clin. Investigation **31:** 370 (April), 1952.

The thiocyanate ion, which had been used extensively for extracellular fluid volume estimation has been found to be bound to albumin in human serum and, therefore, not uniformly distributed throughout the compartment. Furthermore, it is known to penetrate the red cells and values for "thiocyanate space" may include the water of the red cell mass. Studies using a dialysis method on the distribution of thiosulfate is reported in this paper. It was found that thiosulfate is not appreciably bound by the nondiffusible components of human serum and it does penetrate the human red cells. A portion of injected thiosulfate is metabolized and excreted as sulfate. Thiosulfate is excreted by the glomerulus since its appearance is identical with that of inulin. Figures for thiosulfate space are in fairly close agreement with inulin space measurements. It is nontoxic and may be useful for estimating the size of "extracellular fluid" volume.

WAIFE

Frank, A., Metz, D., and Ostendarp, N.: Clinical Observations to the Question of Thermoreceptive Cardiac Reflexes. Zeitschr. Kreislaufforsch. **41:** 417 (June), 1952.

The authors studied in normals and in cardiac patients the effect upon the electrocardiogram of a quantitated cold stimulus applied to the lower extremities. Immersion of the legs into water of 10 to 12 C. for 20 seconds was followed in most of the examined cases by increase of the heart rate and of the amplitude of the deflections in the electrocardiogram. These changes were particularly marked in persons with signs of sympathetic stimulation. In some of the cases with abnormal control electrocardiograms the following changes occurred: lowering of the T wave, occasional depression of the S-T segment, auricular or ventricular premature beats and occasional onset of auricular fibrillation.

The experiments are considered by the authors to confirm the existence of specific thermoreceptive peripheral reflex mechanisms acting upon the heart, which may be responsible for some anomalies found in the electrocardiogram.

PICK

Hoffman, B. F., Siebens, A. A., and Brooks, C. McC.: Effect of Vagal Stimulation on Cardiac

Excitability. Am. J. Physiol. **169:** 377 (May), 1952.

Twenty maximal shocks per second (duration 0.05 to 12.0 millisecond) do not change the diastolic threshold of a dog's auricle when applied to the vagus. Auricular conduction rates were increased (latency unchanged), absolute refractory period shortened and thresholds lowered during the relative refractory period by strong vagal stimulation. Vagal stimulation made the auricle much more likely to fibrillation after single shocks. Repolarization is accelerated by vagal stimulation. Monopolar and bipolar bioelectric currents are decreased in amplitude. Vagal excitation did not change ventricular excitability or conduction velocities. The authors point out similarities in these experiments to those seen when concentration of extracellular Na^+ is low.

OPPENHEIMER

Opdyke, D. F.: Effect of Changes in Initial Tension, Initial Volume and Epinephrine on Ventricular Relaxation Process. Am. J. Physiol. **169:** 403 (May), 1952.

In the light of these experiments with an isolated heart preparation an increase of initial tension, length, systolic tension, and metabolic rate do not change the duration of ventricular relaxation. Epinephrine shortens the duration of relaxation.

OPPENHEIMER

Gunther, B., and Landis, E. M.: Cardiac Resistance to Flow; Pressure Flow Relationships in Quiescent and Beating Turtle Heart. Am. J. Physiol. **169:** 412 (May), 1952.

Hearts relaxed by perfusion with saline solution gave almost linear pressure flow relationships. On the average the pressure-output relationship was 0.9 mm. saline per milliliter per minute. Perfusion with calcium or barium chloride produced a contracture. Now a yield pressure was present and because of the plasticity of heart muscle the pressure–flow curves were changed. When barbiturates were added the heart again became quiescent. This permitted the evaluation of how much cardiac muscular activity covered up the internal resistance of the heart to flow. Work required to overcome internal resistance was compared to external pressure–volume work and to useful work. These comparisons varied with cardiac output and arterial pressure.

OPPENHEIMER

Boucek, R. J., Grindlay, J. H., and Burchell, H. B.: Experimental Constriction of Inflow Tracts in the Heart: Analysis of Circulatory Failure. Am. J. Physiol. **169:** 442 (May), 1952.

When the right inflow tract was constricted there resulted an elevation in peripheral venous pressure, marked ascites, but usually no pulmonary congestion. Constriction of the left inflow tract produced pulmonary congestion with only small increases in peripheral venous pressure. Ascites was absent. In this type there was increased blood volume. This increase in volume was accompanied by pulmonary congestion and edema. It is suggested that when the right inflow tract is constricted the liver produces increased amounts of lymph which may participate in the production of ascites. Two years after the left inflow tract was obstructed it was possible to demonstrate medial hypertrophy of the small muscular pulmonary arteries. Arterioles showed intimal thickening under these circumstances.

OPPENHEIMER

RHEUMATIC FEVER

Hart, F. D., and Husain, O. A. N.: Acute Fatal Rheumatic Fever in an Adult. Lancet **6716:** 1000 (May), 1952.

Acute fulminating rheumatic fever proving fatal in the first attack within a month of acute onset is rare at any age; in middle age it is extremely so.

Although the most likely diagnosis during life was acute rheumatic fever, the failure to respond to both salicylates and antibiotics and the patient's indefinite state of ill health in previous years brought to mind various members of the collagen group of diseases, especially polyarteritis nodosa and lupus erythematosus. No such lesions, however, were found.

The histologic picture in the heart was extremely florid and acute, in keeping with the clinical course, though it is well known that histologic activity does not always imply clinical severity.

BERNSTEIN

Asid, M.: The Antistreptolysin Titer in the Serum. Acta Clin. Belg. **7:** 262 (May–June), 1952.

In 104 patients with various diseases 180 determinations of the antistreptolysin titer in the blood serum were made in order to assess the diagnostic value of the test. The technic used is described in detail. The titer was high in most cases of acute rheumatic fever and was usually normal in cases with chronic polyarthritis and in other nonrheumatic types of joint disease. The titer was elevated following acute tonsillitis, in erythema nodosum and in acute nephritis, and was found normal in cases of chronic nephritis. The author concludes that an elevation of the antistreptolysin titer above normal (200 units) is significant and may be considered as characteristic of an infection with hemolytic streptococcus.

PICK

Simon, A. J., Mack, I., and Rosenblum, P.: Accelerated Rehabilitation in Rheumatic Fever. Am. J. Dis. Child. **83:** 454 (Apr.), 1952.

The authors discuss a program of accelerated rehabilitation of children recuperating from rheu-

matic fever. Mobilization is begun as soon as there is clinical and laboratory evidence that the rheumatic process is quiescent. The authors believe such mobilization not to be injurious to the heart. There were 239 patients (immediate convalescents) followed, 206 of whom were available for comparative study. The control group (postconvalescents) consisted of children most of whose activities had been restricted by their physicians or parents long after the attack of rheumatic fever had ended. Many of these children were "cardiac cripples" by restriction and anxiety rather than by organic heart disease. The patients and controls were followed from one to four years. Subjects were classified as better, the same, or worse at the time of the follow-up depending upon the presence of significant heart murmurs and changes in size of the heart on fluoroscopy. Only diastolic murmurs and systolic murmurs Grade III or more in intensity were regarded as significant murmurs. There were 114 recent convalescents who were better or unchanged, whereas in the postconvalescent group there were 37 better or unchanged and 19 worse. The authors state that the number of patients investigated to date are too few for statistical treatment. Twenty-four per cent of recent convalescents and 34 per cent of postconvalescents were found to be worse. Although it cannot be statistically proved that accelerated rehabilitation is of value, the data suggests that it does not harm the heart.

MARGOLIES

Rammelkamp, C. H., Wannamaker, L. W., and Denny, F. W.: The Epidemiology and Prevention of Rheumatic Fever. Bull. New York Acad. Med. **28:** 321 (May), 1952.

Numerous environmental, bacterial and host factors are concerned in the development of rheumatic fever. The data available indicates that many of these factors, for example, latitude, altitude, climate, season, geographic area, crowding, economic factors and age, are of importance in the incidence of rheumatic fever only because they are related to the incidence of streptococcal infections in general. Once a streptococcal infection has become established, host and bacterial factors are most important. The various serologic types of streptococci and the specific type of disease produced by them apparently are not important factors in the development of rheumatic fever. Positive family history, previous attacks of rheumatic fever and altered antibody response to the preceding streptococcal infection appear to be related to an increased attack rate of the disease. At the present time, methods for the prevention of rheumatic fever are aimed at preventing or actively treating streptococcal infections with antibiotic agents and, thereby, preventing the development of rheumatic fever.

SAGALL

McCarty, M.: Present Status of Knowledge Concerning Pathogenesis and Treatment of Rheumatic Fever. Bull. New York Acad. Med. **28:** 307 (May), 1952.

The author reviews the present knowledge of the pathogenesis of rheumatic fever. The concept most widely held is that the initial event preceding the development of rheumatic fever is infection by group A hemolytic streptococci. Due to the many serologic types of the streptococcus repeated infections with this organism are common during the age period in which the highest incidence of rheumatic fever occurs. The streptococci elaborate many extracellular toxins or enzymes, for instance streptokinase (streptococcal fibrinolysin), streptolysin O, streptococcal hyaluronidase, and others, which may possibly participate or initiate the pathologic processes which result in the clinical picture of rheumatic fever. Several of these products are capable of inducing individually specific antibody responses following natural infections. This antigen-antibody mechanism may be involved in the pathogenesis of rheumatic fever. Evidence in favor of this concept is cited, but the author points out that this theory does not answer two problems of the disease, namely, what is responsible for the localization of the injury resulting from antigen antibody reaction and, secondly, a persistence of rheumatic activity in the absence of continuing streptococcal infection. Possible solutions of these problems are discussed but none afford a satisfactory answer. The present status of treatment of rheumatic fever, likewise, is not settled. Most clinicians agree that conservative management is important in the general care of rheumatic patients. Differences of opinion exist regarding the value of salicylates and their effect on preventing cardiac damage. Cortisone and adrenocorticotropic hormone, likewise, may control the symptoms of the disease, but probably have no effect on the basic mechanisms or on the development of permanent damage. These new pharmacologic agents suggest the possibility of hormonal mechanisms in the pathogenesis of the disease or of hormonal control of symptoms resulting from the host reaction to a pathogenic agent.

SAGALL

Arnsø, E., Brøchner-Mortensen, K., and Hastrup, B.: Follow-up Study of Patients with Rheumatic Fever, with Special Reference to Chronic Cardiac and Articular Disease. Acta med. scandinav. **141:** 77 (May), 1951.

The study is concerned with follow-up observations in a group of 194 patients observed over a period of 9 to 23 years. All had typical rheumatic fever but of varying degrees of severity; one patient had chorea as well. Seventy-five per cent were observed initially during the first attack, the rest during a relapse. Sixteen patients died in the hospital during the initial illness; six of these deaths were due

to increasing cardiac insufficiency. Twenty-three patients died during the follow-up period subsequent to discharge from the hospital; death in three was due to rheumatic heart disease and in six others some cardiac disease was present. The remainder died of various disorders unrelated to the heart.

In the follow-up series of patients still living definite evidence of rheumatic heart disease was present in 9 per cent and possible heart disease in an additional 6 per cent. This is said to correspond to other observations in Scandinavian countries and suggests that the prognosis in rheumatic fever is more favorable in Denmark than in England or the eastern section of the United States. The age distribution in this group of patients was distinctly higher than that of many similar series observed in the United States. Ninety-one of the patients were studied regarding subsequent articular abnormalities. Objective articular manifestations were present in one-fourth of the patients who were followed but in most cases the symptoms were only moderate.

ROSENBAUM

ROENTGENOLOGY

Elkin, M., Sosman, M. C., Harken, D. W., and Dexter, L.: Systolic Expansion of the Left Auricle in Mitral Regurgitation. New England J. Med. **246:** 958 (June), 1952.

Left auricular enlargement, observed roentgenographically, tends to be greater in the presence of both mitral regurgitation and stenosis than in pure mitral stenosis, but this is only a matter of degree and, therefore, of limited clinical value. Expansile pulsation of the left auricle, particularly as seen fluoroscopically in the right anterior oblique position with increased posterior displacement of the barium-filled esophagus occurring synchronously with inward (systolic) movement of the ventricular border, is an important sign of mitral regurgitation. It has been observed in a case of mitral insufficiency resulting from rupture of a mitral chordae tendineae and in direct observations in animals in which mitral insufficiency was created surgically.

There are several factors, however, which influence a changing contour of the left auricle. They include: (a) posterior displacement of the cardiac border, as visualized in the right anterior oblique position, by systolic thickening of a large right ventricle or transmitted pulsation from a vigorously expansile right auricle; (b) alteration of the magnitude of ventricular systolic expansion of the left auricle depending upon the intra-auricular pressure, elastic stretch of the auricular muscle, auricular dilatation and irregular auricular rhythm; (c) a mural thrombus in the auricle.

The workers found two positions valuable for the study of this phenomenon: (a) the anteroposterior view in those cases with a "double contour" of the right cardiac border in which cases a "see-saw" motion with outward bulging of the left auricle and inward motion of the right auricle occurs, and (b) the right anterior oblique position in which the "see-saw" motion involves the expanding left auricle and the contracting ventricular border.

Twenty-nine consecutive patients who showed this fluoroscopic sign were studied clinically and at the time of valvuloplasty. The clinical diagnosis of mitral insufficiency was considered in eight of them, but the surgeon felt a regurgitant jet in 14 cases. In the 14 cases with a palpable regurgitant jet the clinical examination had disclosed no systolic murmur in five, a grade I systolic murmur in 1, a grade II systolic murmur in four, a grade III murmur in three and a grade IV murmur in one. Of the eight cases diagnosed as having mitral insufficiency by clinical standards, the palpable jet was absent in three. It is emphasized that the blood pressure plays a significant role in the production of a palpable jet and the diagnosis of mitral insufficiency is not excluded if the blood pressure is very low or imperceptible at the time of valvuloplasty. It is emphasized also that although the demonstration of systolic expansion of the left auricle at careful fluoroscopy is a valuable sign of mitral insufficiency, the absence of this sign does not have any great diagnostic significance.

ROSENBAUM

SURGERY IN HEART AND VASCULAR SYSTEM

Maurer, E. R.: Successful Removal of Tumor of the Heart. J. Thoracic Surgery **23:** 479 (May), 1952.

A case is reported of the successful removal of a large primary lipoma of the heart (3.5 pounds) in a 44 year old male. Through the use of angiocardiography, a preoperative diagnosis of a pericardial coelomic cyst was made. At operation the tumor was found to be attached to the anterior surface of the left ventricle by a common stalk. The point of attachment of the lipoma was separated from the ventricular wall, being followed by a moderate amount of brisk bleeding which was controlled with warm moist compresses. The postoperative course was uneventful.

ABRAMSON

Andreasen, A. T., and Watson, F.: Experimental Cardiovascular Surgery. Brit. J. Surg. **39:** 548 (May), 1952.

This paper records the preliminary results of a series of experiments, the object of which was to define the conditions under which immediate and remote survival of dogs occurs after temporary caval occlusion. The series forms the first part of a research into the possibility of obtaining a "dry heart" for intracardiac surgery. Maintenance of the small flow through the azygos vein, with the cavae clamped, is sufficient to maintain the brain

and heart without detriment to full functional recovery in dogs over a period of at least 35 minutes.

BERNSTEIN

Stead, W. W., and Soucheray, P. H.: Physiologic Studies Following Thoracic Surgery: I. Immediate Effects of Thoracoplasty. J. Thoracic Surg. **23:** 453 (May), 1952.

The authors studied the physiologic effects noticed within 24 hours of each stage of the three-stage thoracoplasty in 10 human subjects suffering from cavitary pulmonary tuberculosis. Preoperative studies revealed a significantly greater index of pulmonary mixing and residual volume in these patients than in a group of normal individuals.

In each instance postoperatively there was a mild degree of anoxemia, probably related to the finding that there was passage of blood through the pulmonary bed without exposure to alveolar air. The pulmonary shunt was considered to be due to continued perfusion of recently collapsed pulmonary tissue. There was also an increase in metabolic rate accompanied by a proportionately greater augmentation in respiratory minute volume.

It was concluded that a chest whose expansion is limited by pain following surgical manipulation is required to maintain a slightly greater alveolar ventilation than it did preoperatively. This demand is met by an increased respiratory rate.

ABRAMSON

Denolin, H., De Coster, A., Dumont, A., and Cautinieaux-Duwaerts, S.: Cardiovascular Alterations Following Pneumonectomy. Acta cardiol. **7:** 261 (Fasc. 3), 1952.

The authors present electrocardiographic and cardiorespiratory studies on patients submitted to pneumonectomy. In 27 cases electrocardiograms were recorded during surgery and remained without significant alteration in the moment of closure of one pulmonary artery. This was in accord with the results of experiments performed on dogs, in the course of which right ventricular pressure and cardiac output did not change following ligation of the left pulmonary artery. During the first days following pneumonectomy, auricular fibrillation and flutter frequently developed, especially in patients over 40 years of age who manifested a tendency to pulmonary edema. The mechanism of this association of circulatory disturbances is obscure and number of factors may be responsible. During the same period a deviation of the electrical axis was observed in the electrocardiogram, apparently related to a change of the position of the heart. However there were never changes characteristic of acute cor pulmonale.

Fourteen patients were studied 1 to 30 months after pneumonectomy. Frequently there was an increase of the residual air and of total lung capacity and a decrease of the maximal breathing capacity and of the usable portion of the vital capacity. Exercise was poorly tolerated, leading to hyperventilation and reduction of the respiratory reserve. The arterial oxygen saturation remained normal, the cardiac output was normal or slightly increased. The pressure in the right ventricle and in the pulmonary artery increased slightly in several cases; this is ascribed to alterations in the vessels in the remaining lung or to restriction of their capacity by distension of the remaining lung tissue.

The authors conclude that the cardiopulmonary behavior following pneumonectomy is extremely variable. They recommend detailed functional respiratory and cardiodynamic studies in patients to be submitted to this type of surgery.

PICK

Linton, R. R., and Hardy, J. B., Jr.: Treatment of Thoracic Aortic Aneurysms by the "Pack" Method of Intrasaccular Wiring. New England J. Med. **246:** 847 (May 29), 1952.

The results of treatment of thoracic aortic aneurysms by a new "pack" method of intrasaccular wiring are reported in this publication. There was a total of 18 patients with 24 aneurysms. All but one of the aneurysms were fusiform in type and all but one were syphilitic in origin. These workers have developed a technic whereby much greater lengths of wire than previously employed are introduced in an effort to strengthen the wall of the aneurysmal sac at all points. Lengths of wire ranging from 30 to 500 feet were used in these patients, the mean amount being 229 feet. The wire was a stainless-steel alloy, 30 gage or 0.010 inch in diameter, which was roughened with emery cloth before sterilization to increase its surface area and increase thrombus formation. In eight instances an indirect method was used, inserting the wiring trocar through a small skin incision in the thoracic wall without visualizing the aneurysm, and in 10 cases the aneurysm was exposed by thoracotomy allowing a direct method of wiring. Experience proved the direct method to be preferable except in those patients who are too ill to withstand opening of the chest and in whom the aneurysm lies directly beneath the thoracic wall.

Sixteen patients survived the operation and lived sufficiently long to evaluate the results of this type of therapy. Fifty per cent of the patients had complete relief of pain and dyspnea and nearly all of the others were at least partially relieved of these symptoms. Subsequent rupture of the aneurysms was still the most common cause of death, but the authors report that no patient in whom wiring was considered adequate performed by the direct method had died of rupture at the time of their report. It was felt that life was prolonged in 61 per cent of the patients treated. The longest survival after operation was six years and three months. It is emphasized that wiring should be performed early in the course

of the disease before the lesion becomes large enough to obstruct the trachea.

ROSENBAUM

Cooley, D. A., and De Bakey, M. E.: Surgical Considerations of Intra-Thoracic Aneurysms of the Aorta and Great Vessels. Ann. Surg. **135:** 660 (May), 1952.

The authors review and evaluate the various methods employed in the surgical treatment of intrathoracic aneurysms of the aorta and its major branches. One group consists of various means to promote thrombosis and fibrotic organization. Into this category fall such procedures as attempts to diminish the blood pressure or retard the velocity of circulation, steps to increase the coagulability of the blood, and the use of agents to provoke thrombus formation within the sac by acting directly on the aneurysmal tissues. Clot formation can be induced by such means as ligation, introduction of foreign material, and stimulation of periarterial fibrosis.

Another method of treating this condition is endoaneurysmorrhaphy involving either obliterative, restorative or reconstructive steps. However in the case of intrathoracic aneurysms, this approach is not readily applicable. Finally, excision has been attempted, but this procedure is also very difficult to carry out in the case of lesions of this type. Nevertheless, it is the authors' opinion that extirpation, preferably with restoration of normal blood flow, is the method of choice.

ABRAMSON

Peck, M. E., and Grover, R. F.: Cardiovascular Responses to Acute Ligation of the Portal Vein. Arch. Surg. **64:** 665 (May), 1952.

An attempt was made to determine the underlying physiologic mechanism which provoked the changes in arterial blood pressure following ligation of the portal vein in dogs. The receptors present in the splanchnic mesentery seemed to be implicated in the initial drop in pressure, the response being reflex in nature. The secondary fall was considered to be due to blood volume alterations.

ABRAMSON

THROMBOEMBOLIC PHENOMENA

Leonard, F. C., and Cogan, M. A.: Failure of Ligation of the Left Auricular Appendage in the Prevention of Recurrent Embolism. New England J. Med. **246:** 733 (May 8), 1952.

Two patients with rheumatic heart disease, mitral stenosis and auricular fibrillation are reported. One of them treated with continuous Dicumarol was well without re-embolism for 22 months. The second patient underwent ligation of the left auricular appendage, said by these writers to be the fourth such procedure reported in the literature. Recurrent embolism occurred on the eighth and again on the ninth postoperative days. It is said that in previous reports of pathologic observations in patients with rheumatic heart disease and systemic embolism, only 26 per cent of the patients had thrombi limited to the left auricular appendage. These authors believe that until intracardiac thrombi can be better localized, preventive appendage surgery should be abandoned in favor of anticoagulant methods.

ROSENBAUM

Trimble, I. R., and Lynn, D. H.: Elastic Compression in the Prophylaxis of Postoperative Thrombo-Embolism: A Critical Study. Ann. Surg. **135:** 681 (May), 1952.

The authors attempted to assay the possible prophylactic use of elastic bandages in preventing thromboembolic episodes in susceptible individuals. The study was carried out on 392 surgical patients burdened with advanced age, obesity, heart disease, carcinoma, blood disorders, antecedent thromboembolism and arterial insufficiency. Of this number, only seven manifested clinical evidence portending the presence of thromboembolism, an operative incidence of 1.47 per cent.

It was felt that although the use of elastic bandages appeared to reduce the incidence of thrombotic episodes, further trial with this method was indicated before definite conclusions regarding its efficacy could be reached.

ABRAMSON

Pool, R. M., and Farrar, T.: Aortic Embolectomy. Ann. Surg. **135:** 655 (May), 1952.

The authors reported a case of successful aortic embolectomy, carried out within several hours after embolism had occurred. The transabdominal approach was used and anticoagulants were instituted immediately following the operation. Postoperatively, repeated caudal blocks were performed because the circulation in the left leg was precarious. Since the temporary response to such a procedure was good, a lumbar sympathectomy was carried out. Follow-up examinations over a period of 22 months postoperatively revealed no further change in the state of the lower extremities.

ABRAMSON

VASCULAR DISEASE

Orr, K. D., and Fainer, D. C.: Cold Injuries in Korea During Winter of 1950–51. Medicine **31:** 177 (May), 1952.

Cold injuries include frostbite (ground type and high altitude frostbite) and the trench foot–immersion foot syndrome. These types of injuries have a similar clinical appearance, and under combat conditions, a mixture of trench foot and frostbite is common. By the time the patients were seen, the affected part had generally been rewarmed, and it was difficult to determine whether actual freezing

of the tissues had taken place. The authors reviewed the records of 2,257 cases admitted to a special Army hospital serving as a center for cold injuries.

Frostbite is classified into four degrees of severity, and all degrees may be present in a part, the distal portion being most severely injured. First degree frostbite involves the superficial layers of skin and is characterized by numbness, erythema, swelling and desquamation. Second degree injuries produce vesiculation, and do not involve subcutaneous tissues. Third degree frostbite involves the entire thickness of the skin and extends into subcutaneous tissues, with or without vesicles. Fourth degree frostbite extends into the entire thickness of the part including bones, and results in loss of the part. There are few or no vesicles. The sites of injury are generally the extremities, chiefly the feet.

The incidence of frostbite among smokers and nonsmokers was compared, and no significant statistical difference was demonstrated. The incidence was higher among Negro troops than white troops.

The physiopathology of frostbite is not entirely clear, but it is certain that there is an important vascular component. During the chilling period peripheral vasoconstriction is present. After rewarming hyperemia occurs, and the part becomes edematous and vesicles and bullae appear. Thrombosis may occur, with resulting gangrene which may be dry or wet (secondarily infected).

The clinical manifestations depend upon severity of injury, and early management. The onset of freezing is not particularly painful and is associated chiefly with numbness. After rewarming, swelling begins in less than three hours, and vesiculation within the next day. Immediately after rewarming, even the most severely injured parts became warm. First degree frostbite generally healed within a month, though hyperhidrosis and a feeling of coldness often persisted. Second degree frostbite required up to 36 days for peeling of the vesicles. Several weeks after the injury, hyperhidrosis and coolness was noted. Third degree frostbite was associated with pain beginning some days after injury, and lasting up to two months. The ulcerations healed on the average in 68 days, and hyperhidrosis and coolness were observed between the fourth and tenth weeks. The healing time of fourth degree frostbite depended upon the type and course of gangrene, and it was not possible to predict whether wet or dry gangrene would occur until 12 to 34 days following injury.

Initial treatment should consist of removing constricting clothing, and rewarming by exposure to room temperature (70 to 78 F.), or by contact with a warm part of the body. General body warmth must be maintained. Pressure and petrolatum dressings must be avoided, only loose dry dressings being applied; vesicles and bullae must be protected and not drained. Tetanus toxoid boosters and penicillin should be given early. Hospital treatment should consist of bed rest with slight elevation of the foot of the bed, and exposure of injured parts to room air at temperatures between 70 and 78 F. Smoking should be forbidden, and physiotherapy instituted early.

Several new procedures in treatment were used, including intravenous procaine, sympathetic ganglion blocks, priscoline, and heparin. No agent was clearly demonstrated to prevent gangrene. However, the impression was gained that loss of tissue was minimized in cases treated with heparin, in which treatment was begun within 36 hours after rewarming.

ENSELBERG

Scott, Michael: Cerebral Apoplexy Due to Spontaneous Intracranial Hemorrhage. J. A. M. A. **149:** 129 (May 10), 1952.

This article reports 23 consecutive cases of surgically treated spontaneous nontraumatic intracranial hemorrhage between the ages of 25 to 70. Eight patients died in the hospital after operation; 15 patients recovered from the acute episode and were discharged. Spontaneous intracranial hemorrhage produces symptoms and signs of a focal expanding lesion and is associated in the majority of cases with bloody spinal fluid under increased pressure. It is important to differentiate it from cerebral thrombosis or embolism because treatment with stellate block or with anticoagulants might prove disastrous if used in hemorrhage. The author feels that any person regardless of age, experiencing sudden headache associated with focal signs such as aphasia, visual field defect, anesthesia, hemiplegia and progressive drowsiness or stupor should be considered to have a space taking lesion which may be intracerebral hematoma. He recommends a careful history and neurologic examination, examination of the eyegrounds, careful spinal puncture to determine pressure and slow removal of 3 cc. fluid in search for evidence of bleeding and stereoscopic x-ray examination of the skull for determination of pineal shift. It is not felt that cerebral angiography is essential and the diagnosis and location of the clot was established in every case in this series without it. Occasionally patients with intracerebral hemorrhage recover spontaneously but the majority show progression in focal signs and increased intracranial pressure and will die unless prompt diagnosis and surgical intervention is instituted. An addendum to the article reports seven additional patients, of which two died and five recovered.

KITCHELL

Cholst, M. R., Levitt, L. M., and Handelsman, M. B.: Small Vessel Dysfunction in Patients with Diabetes Mellitus: II. Retinal Vessel Response in Diabetics Following Priscoline. Am. J. Med. Sci. **224:** 39 (July), 1952.

Measurement of the degree of dilatation of retinal vessels was made by the use of angioscotometry which is the tracing out of bands of physiologic blindness corresponding to the retinal blood vessels. Following the injection of Priscoline a marked widening of the angioscotoma was noted in control subjects. However, in 12 of 28 diabetic patients studied, there was demonstrated an inability of the retinal vessels to dilate maximally as determined by poor widening of the angioscotomata after Priscoline injection. Vascular sclerosis was absent in the diabetics; however, those manifesting poor responses were found to have perimacular exudation of the diabetic type. There was no correlation between the small vessel dysfunction observed in the retinal vessels and that shown to occur in the skin of the toes.

SHUMAN

Lowman, E. W., and Slocum, C. H.: The Peripheral Vascular Lesions of Lupus Erythematosus. Ann. Int. Med. **36:** 1206 (May), 1952.

In lupus erythematosus, a vascular pattern of reaction on the venous side of the circulatory system appears to consist of three successive phases: edema, cellular reaction and sclerosis. The edematous stage of phlebitis was noted in two cases of lupus erythematosus and in one of the control group, the latter a case of operative shock. The cellular reactive phase, consisting of residual swelling and thickening of the venous wall, together with a cellular reaction of large mononuclear and lymphocytic cells, was noted in some muscle in all cases of lupus erythematosus and in nerves from 93 per cent of the cases. It would appear that the polymyositic and perineuritic nodules of lupus erythematosus are identical to those seen in rheumatoid arthritis, and that both are produced in this vascular pattern of reaction. Synovial changes noticed were vascular and identical to the pattern of reaction seen in other tissues; in addition, the stroma showed initial edema with subsequent fibroblastic response and fibrosis. Synovial lining cells showed only mild hyperplasia. In cases of lupus erythematosus, the vascular reaction identical in nature to that previously observed in cases of rheumatoid arthritis and the similarity of the reaction to that seen in periarteritis suggest a common pathologic factor. There is no clue as to whether the reaction pattern is secondary to damage by an extraneous factor, or whether a hyperergic response is effecting injury to a responding system.

WENDKOS

OTHER SUBJECTS

Tourniaire, A., Tartulier, R., and Deyrieux, F.: Modifications in the Evolution of Acute Cor Pulmonale. Arch. mal. coeur **45:** 448 (May), 1952.

Acute cor pulmonale due to pulmonary embolism does not always take a fatal course and recovery may be rapid and complete. In other cases repeated embolization, or thrombosis superimposed on the primary embolus, may produce a subacute clinical entity, characterized by fever and right heart failure, which sometimes may subside, but frequently is progressive and resistant to treatment.

The author observed three cases of the latter variety and presents their clinical data, and autopsy findings in two of them. In the first patient who recovered, the diagnosis of subacute cor pulmonale was established following a typical attack of pulmonary embolism, originating in thrombosed leg veins, accompanied by typical electrocardiographic findings and followed by the development of right heart failure and roentgenologic enlargement of the right ventricle. The second had a similar clinical course but died. Autopsy revealed generalized thrombosis of the pulmonary arteries. The third case showed at x-ray examination multiple infiltration and increased vascular markings of the left lung, while the right lung field was clear. This was explained by the autopsy findings which revealed a massive embolus in the right main pulmonary artery and multiple thromboembolic changes in more peripheral segments of the left pulmonary artery.

PICK

Anderson, M. W., Kelsey, J. R., Jr., and Edwards, J. E.: Clinical and Pathological Considerations in Cases of Calcific Aortic Stenosis. J. A. M. A. **149:** 9 (May 3), 1952.

Calcific aortic stenosis is an entity of clinical significance encountered frequently in the practice of internal medicine. Because this lesion is largely found in middle life or old age, and now longevity has been increased markedly, it is met quite often. The article presents 49 cases with calcific aortic stenosis demonstrated at necropsy. There were 41 men and eight women. The average age at death was 63.4 years with a range of 39 to 90 years. Angina pectoris occurred in 40.8 per cent of the cases and of these cases of angina 55 per cent had severe degrees of aortic stenosis and mild coronary sclerosis. Thirty per cent had mild aortic stenosis and severe coronary sclerosis. Of the 29 patients who did not have angina, 55.2 per cent had severe aortic stenosis with mild coronary sclerosis and only 6.9 per cent had mild aortic stenosis and severe coronary sclerosis. Clinical diagnosis of 12 episodes of myocardial infarction was supported by positive pathological findings in only four cases and the electrocardiogram was diagnostic in only three of these four. This discrepancy has been attributed to the reversible nature of prolonged myocardial ischemia. Myocardial failure occurred in 36 cases (73.5 per cent). It had an average duration of two and two-tenths years before death. Abnormal electrocardiograms were recorded in 42 of 47 cases. The patterns

of electrocardiographic abnormality most frequently noted were left ventricular hypertrophy and left bundle branch block. Auricular fibrillation occurred infrequently. In spite of many associated diseases the terminal event in 28 of the 29 patients was chronic or acute cardiac failure. In six additional cases death was sudden and presumably of cardiac origin.

KITCHELL

Aviado, D. M., Jr., Cerletti, A., Alanis, J., Bulle, P. H., and Schmidt, C. F.: Effects of Anoxia on Pressure, Resistance and Blood (P^{32}) Volume of Pulmonary Vessels. Am. J. Physiol. **169:** 460 (May), 1952.

Pulmonary arterial pressure was found to be elevated in anesthetized dogs breathing 5 to 10 per cent oxygen. The authors are of the opinion that this can best be explained by chemoreceptor reflexes from the carotid and aortic bodies along with epinephrine release. These two factors increase pulmonary flow. In these experiments pulmonary vessels respond to anoxia by local dilation. No evidence of construction was found. Despite a local dilation of pulmonary vessels during anoxia pulmonary arterial pressure and blood volume are increased because of the increased pulmonary blood flow.

OPPENHEIMER

Palfrey, T. W.: Management of Dyspnea. New England J. Med. **246:** 826 (May 22), 1952.

The writer points out that cardiac dyspnea results from an imbalance between muscular exertion and deficient cardiorespiratory function. The walking and climbing method of the Swiss mountaineers is described. It is reported that the Swiss guide walks with steps as regular as the ticking of a clock about 100 to the minute and at a constant rate and rhythm all day. The length of the step is whatever is natural for the walker with shortening as the grade increases but still at the constant rate and rhythm. The author reports that a considerable number of his patients have benefited from learning to walk in this fashion.

ROSENBAUM

Walsh, J. R., and Egan, R. I.: The Reliability of the L. E. Test. New England J. Med. **246:** 775 (May 15), 1952.

In order to test the specificity of the plasma L. E. phenomenon, these observers studied the plasma of 25 patients, four of whom had systemic lupus erythematosus and five of whom had discoid lupus erythematosus. The test was positive only in the four patients with systemic lupus erythematosus. The plasma of each patient was consistently positive in two to seven different marrows. Plasma from patients with discoid lupus erythematosus, rheumatic fever, rheumatoid arthritis, periarteritis nodosa, multiple myeloma, nephritis, erysipelas, contact dermatitis and chronic eczematoid dermatitis was consistently negative. Intensive cortisone therapy of systemic lupus erythematosus did not change significantly the results of the test. A suggestion of prognostic significance of the test was obtained in one fulminating case in which the L. E. plasma test was strongly positive and death occurred while the patient was on cortisone therapy.

ROSENBAUM

Broida, H. P., Freis, E. D., and Rose, J. C.: A Variable Heart Pump Permitting Independent Control of Rate, Output, and Ejection Velocity. Science **115:** 603 (May 30), 1952.

This report describes a diaphragm pump which is driven by a variable speed motor and containing a driving cam so shaped that the discharge characteristics of the pump are similar to those from the heart. This pump may be used to replace either the right or the left ventricle, leaving the lumgs and opposite chamber of the heart to function normally. This device permits wider flexibility in physiologic studies, in that it is a useful method of separating the peripheral from the cardiac actions of agents that effect the cardiovascular system.

WAIFE

White, James C.: Conduction of Visceral Pain. New England J. Med. **246:** 686 (May 1), 1952.

The viscera as well as other deep structures require massive stimuli because of their poor supply of pain-conducting fibers. The high threshold of viscera to pain is lowered during inflammatory states. Although the internal organs have a definite sensitivity to pain, the threshold is high and the localization poor. Localization of visceral pain is poor because man has comparatively little experience with visceral pain and does not build up an elaborate cortical projective pattern. Furthermore, visceral pain is poorly defined and is usually only a dull aching discomfort because the deep structures have none of the differentiated nerve endings which are capable of appreciating temperature or touch. Experience during cardiac and splanchnic denervation in man has shown that in all the sympathetic trunks to the abdominal organs, kidney, ureters and uterine fundus, pain can be interrupted most safely and effectively by specific sympathetic denervation. In cases of angina pectoris and aortic aneurysm in which visceral pain enters the cord over a small number of spinal segments, relief may be effected by cutting the posterior (sensory) spinal roots. Intractable visceral pain may also be relieved by anterolateral cordotomy. There are no characteristic features of visceral pain that set it apart from pain arising in deep somatic structures.

ROSENBAUM

BOOK REVIEWS

Atlas d'Électrocardiographie avec des Notions de Vectocardiographie à l'Usage du Médicin Praticien et de l'Étudiant, ed. 3. *F. Fattorusso and O. Ritter.* Paris, Masson et Cie, 1952. 265 pages, 230 figures. 3200 fr.

The third French edition of this atlas of electrocardiography "for use by the practitioner and student" has been thoroughly revised and amplified. Many errors present in previous editions have been corrected and valuable material added pertaining to more recent trends in clinical electrocardiography. As before the volume is divided into two parts. The first, the more practical part, deals with the normal and abnormal electrocardiogram. Particularly stressed is the differentiation of physiologic alterations (e.g., childhood, Q_3) and pathologic alterations of the ventricular complex. Arrhythmias are considered in fundamental principles. The second, the theoretic part, deals with basic electrophysiology as applied to the explanation of electrocardiographic leads and patterns, and with the concept of the ventricular gradient. In an amplified chapter on vectorcardiography, which includes a recapitulation of fundamentals in trigonometry, the advantages and limitations of the method are pointed out very ably.

A clearly and concisely written text faces numerous excellent diagrams and well chosen illustrations of actual electrocardiograms. The latter are, in great part, exact copies of figures taken from the recent American and French literature. The diagrammatic representation of posterolateral wall infarction (fig. 100) requires correction to avoid confusion. Objection could also be raised to the author's definition of focal intraventricular block and to statements concerning contraindications to quinidine therapy.

As a whole, the book represents a valuable contribution to the literature on basic electrocardiography. It will familiarize the European as well as the American reader with advances made inside and outside his continent and is well suited to serve the purpose stated in its title.

A. Pick

Circulatory Dynamics. Physiologic Studies. *Carl J. Wiggers.* **Modern Medical Monographs. No. 4.** New York, Grune & Stratton, 1952. 116 pages, 44 figures. $4.00.

Although the culmination of a successful research career carries no legal obligation to synthesize one's knowledge for the benefit of fellow investigators and practitioners, it is always gratifying to encounter such an offering. Dr. Wiggers, dean of American cardiovascular physiologists, continues his service in this three chapter monograph.

Chapter one is devoted to a simple exposition of basic hemodynamic principles with emphasis on their application to man. The arterial pressure pulse, its transformation and factors affecting systolic and diastolic pressure are briefly, but concisely, covered. A discussion of the arterial dynamics of hypertension serves to illuminate the concept of peripheral resistance. The material in this chapter is solid foundation and will be of great value to the practitioner and novice investigator. It will be regarded lightly only by the supercilious cardiologist.

Dr. Wiggers discusses the determinants of cardiac performance in the second chapter. He reviews authoritatively the investigations which led to the concept of "the law of the heart" and integrates the factors of initial length and initial tension in the control of cardiac behavior with great skill. The result of this analysis is, as Dr. Wiggers states, "that very old laws of cardiac behavior have merely been given more extended applications, rather than that essentially new ones have been discovered." Exceptions will be taken to this conclusion, of course, but those who differ will do well to ponder on this chapter at some length.

The third chapter covers the dynamics of ventricular contraction under a variety of abnormal conditions, including hypertension, coarctation, stenoses, insufficiencies, ventricular alternation, coronary occlusion, and pericardial effusion. The chapter is introduced by a short discussion on the technics of recording and interpreting ventricular pressure pulses. Clinical cardiologists will appreciate the correlation of the results of experimental studies with clinical problems.

David F. Opdyke

Transactions of the American College of Cardiology. Volume 1—1951. *Edited by Bruno Kisch.* New York, American College of Cardiology, 1952. 138 pages, 35 figures, 3 tables.

This volume presents the papers read at "The First National Meeting of the American College of Cardiology" held at the Statler Hotel, New York City, on Oct. 6, 1951. This represents 13 papers discussing various aspects of coronary artery disease plus tributes to Franz M. Groedel, M.D., and Aaron E. Parsonnet, M.D., deceased, who were instrumental in the organization of this College. The constitution and by-laws of the College are included as is the opening address of the meeting made by

Dr. Bruno Kisch in which the aims of the organization are outlined.

Dr. Paul M. Zoll presented the normal anatomy of the coronary arteries as shown by the injection technic as well as the findings that coronary occlusions occur twice as often in the main stems as in the branches. Multiple occlusions are the rule, with the left descending, left circumflex and right coronary being most often involved. Dr. Donald E. Gregg showed that true coronary dilatation occurs in response to increased oxygen demand, increased metabolites or local anoxia. Dr. W. Raab went on to point out that angina pectoris results from an influx of catecholamines into the heart muscle resulting in an excessive, wasteful oxygen consumption leading to local hypoxia. This may even lead to local necrosis.

Captain Ashton Graybiel, in discussing the symptomatology of coronary insufficiency presented an excellent discussion of the factors affecting the work of the heart, its blood supply and the relation of symptoms to degree of coronary insufficiency. Dr. Carl F. Schmidt, in considering therapy in coronary disease, pointed out that a desirable drug would increase coronary venous oxygen content, saturation or tension. He felt that amyl nitrite, nitroglycerine and papaverine were desirable; tetraethylammonium was without effect, and aminophylline and niketharnide were undesirable.

Dr. Simon Dack presented the electrokymographic findings one might find in coronary artery disease. Drs. A. Grishman and L. Scherlis demonstrated the spatial vectorcardiograms of anterior and posterior myocardial infarctions. Dr. S. H. May felt that the testing of coronary competence by the exercise or the anoxemia test was dangerous, that interpretation of the results of these tests was fallacious and that the tests were not compatible with physiologic principles.

Drs. B. L. Zobman, H. I. Russek, A. A. Doerner, A. S. Russek and L. G. White, felt that history and clinical signs and symptoms are clues to the prognosis in myocardial infarction and not the age of the patient. They also found that Dicumarol did not alter mortality in "good risk" cases. Dr. Kurt Bliss pointed out that, in his opinion, subintimal hemorrhage is a frequent cause of coronary occlusion and that this would contraindicate the use of Dicumarol. Dr. J. B. Wolffe reiterated his belief that atherogenesis may result from pancreatic dysfunction and that coronary artery disease is helped by pancreatic extract. In the paper which concluded the meeting, Dr. A. S. Hyman summarized the more recent ideas on therapy in cardiac arrest.

ARTHUR BERNSTEIN

Pathologie Vasculaire Médicale et Chirurgicale. *Marceau Servelle. Preface by P. Soulie.* Paris, Masson et Cie, 1952. 442 pages, 116 figures. 2800 fr.

The title suggests that medical as well as surgical treatment of vascular diseases is dealt with. The book is written by a surgeon, apparently without the cooperation of an internist except for the chapter on congenital heart diseases, and the treatment recommended is nearly all surgical. A great many internists as well as surgeons interested in vascular diseases will disagree with the indications and dispute the results of many of the recommended operations. They will also disagree with the stand taken by the author rejecting anticoagulant therapy.

In a chapter on arteritis, a term used to cover most arteriopathies, thromboangiitis obliterans is discussed on half a page and rejected as a separate disease entity. Among the arguments for this stand taken by Servelle: "The macroscopic lesions described by Burger are also found in patients of higher age. We have seen arteritis in patients of 20, 25 and 30 years of age, and they were not Jews. Evidence has never been provided of the infectious factor as invoked by that author. This is why we, like our teacher Leriche, range in to the same group the immense majority of juvenile obliterating arteritis." As treatment for "juvenile arteritis" is recommended: sympathectomy, splanchnicectomy, adrenalectomy, endarteriectomy and arterial grafts. The treatment advised for "arteritis of the old" is: arteriectomy and lumbar sympathectomy. Tremendous importance is given to arteriography. The medical treatment is discussed in one and one-half pages and pronounced ineffective. There is no statistical workup of the long range results of these surgical operations and only few case histories are presented.

In the chapter on diseases of the veins venography is declared to be indispensable. Anticoagulants are rejected in the treatment of acute thrombophlebitis. "Uncomplicated cases" are treated with immobilization in bed and lumbar blocks. In "cases complicated with edema" and "cases complicated with edema and cyanosis" venography is performed to determine the type of surgical intervention. In case of edema, extraction of the clot and ligation, if the clot adheres to the wall, is done. The sequelae of phlebitis are treated with vasodilators, elastic bandages, and, if this is unsatisfactory, with lumbar blocks, perivenous sympathectomy and excision of the thrombosed segment with lumbar sympathectomy.

Great importance is given to lymphography. In a chapter written in collaboration with Soulie the diagnosis, operative indications and technic of congenital and acquired heart lesions are rather briefly discussed and described.

ERWIN A. WERNER

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SCIENTIFIC SESSIONS

Following are the titles of papers, panels, and other features scheduled for the Association's Twenty-Sixth Scientific Sessions from Thursday, April 9, through Sunday, April 12, at the Hotel Chelsea, Atlantic City, N. J.

Special Session on Electrocardiography and Vectorcardiography—7:30 P.M., Thursday, April 9

Chairman: Maurice Sokolow, Co-Chairman, Program Committee

1. The Zero-Potential Contour on a Homogeneous Conducting Cylinder. *Ernest Frank and Calvin F. Kay, Philadelphia, Pa.*
2. Right Ventricular Hypertrophy: A Comparative Study in Spatial Vectorcardiography with Cube and Tetrahedron Coordinates, and Quantitative Spatial Summation Vectorcardiography. *William D. Allison, John R. Urbach, David Gelfand and Samuel Bellet, Philadelphia, Pa.*
3. A Correlation of the Spatial Vectorcardiogram with Right Ventricular Hypertrophy. *Stephen R. Elek, Bertram J. Allenstein, George C. Griffith, Richard S. Cosby and David C. Levinson, Los Angeles, Cal.*
4. Membrane and Action Potential of the Cardiac Muscle Fiber with Observations on the Nature of the Electrocardiogram. *Hans H. Hecht, Allan J. Brady, Lowell A. Woodbury and Grant A. Hickman, Salt Lake City, Utah.*
5. The Coronary QR Wave. *Myron Prinzmetal, S. Rexford Kennamer, Clinton M. Shaw, Noboru Kimura, Inga Lindgren, Alfred Goldman, Morton H. Maxwell, Jacob Bernstein and Alfred Breckler, Los Angeles, Cal.*
6. Analysis of the Electrocardiograms Obtained from 1000 Young Healthy Aviators: Ten Year Follow-up. *John M. Packard, John S. Graettinger and Ashton Graybiel, Pensacola, Fla.*
7. Unusual Electrocardiograms before and during Acute Coronary Occlusion and Myocardial Infarction. *Harry L. Jaffe, New York, N. Y.*

First Session—9:00 A.M., Friday, April 10

Co-Chairman: John P. Hubbard and Paul F. Dwan, Council on Rheumatic Fever and Congenital Heart Disease

8. Pulmonic Stenosis: A Physiologic Analysis. *Aaron Shaffer, Earl N. Silber, Gerald R. Graham and Louis N. Katz, Chicago, Ill.*
9. Reactivation of Rheumatic Fever Following Mitral Commissurotomy. *Louis A. Soloff, Jacob Zatuchni, O. Henry Janton, Thomas J. E. O'Neill and Robert P. Glover, Philadelphia, Pa.*
10. Effects of Salicylate Administration on Adrenal Cortical Steroid Secretion. *Vincent C. Kelley, Alan K. Done and Robert S. Ely, Salt Lake City, Utah.*
11. Short Term (Two Weeks) Combined Penicillin-Dihydrostreptomycin Therapy of Subacute Bacterial Endocarditis Caused by Penicillin-Sensitive Streptococci. *Joseph E. Garaci and William J. Martin, Rochester, Minn.*
12. Tetralogy of Fallot with Unilateral Pulmonary Atresia. *Alexander S. Nadas, Harold D. Rosenbaum, Martin H. Wittenborg and Abraham M. Rudolph, Boston, Mass.*
13. Determination of C-Reactive Protein in Serum as a Guide to the Treatment and Management of Rheumatic Fever. *Gene H. Stollerman, Samuel Glick and Dali J. Patel, New York, N. Y.*
14. Localization of Cardiac Defects by Dye Dilution Curves Recorded Following the Injection of T-1824 at Multiple Sites in the Heart and Great Vessels during Cardiac Catheterization. *H. J. C. Swan and E. H. Wood, Rochester, Minn.*
15. Panel Discussion—Prevention of Rheumatic Fever. *David D. Rutstein, Moderator.*

TO BE READ IF TIME PERMITS

16. The Clinical Diagnosis of Mitral Regurgitation. *Walter H. Abelmann, Laurence B. Ellis and Dwight E. Harken, Boston, Mass.*
17. Observations on the Hemodynamics of Eisenmenger's Syndrome. *Franz Kohout, Earl. N. Silber, Jakub G. Schlichter and Benjamin Kaplan, Chicago, Ill.*

Second Session—2:00 P.M., Friday, April 10

Co-Chairman: A. Carlton Ernstene and Wright R. Adams, Section on Clinical Cardiology

18. A Study in the Management of Shock Associated with Acute Myocardial Infarction. *George C. Griffith, W. B. Wallace, Burt Cochran, Jr., William E. Nerlich and W. G. Frasher, Los Angeles, Cal.*
19. Lewis A. Conner Lecture—The Physiology of Cardiac Output. *William F. Hamilton, Augusta, Ga.*
20. Demonstration of a Significant Renal Circulatory Factor in the Edema Formation in Patients with Constrictive Pericarditis. *James W. Culbertson, Walter M. Kirkendall, Johann L. Ehren-*

haft, William H. Ames, Ernest O. Theilen and George N. Bedell, Iowa City, Iowa.

21. Paroxysmal Auricular Tachycardia with Block: An Experimental and Clinical Study of Its Relation to Digitalis and Potassium. *Harold D. Levine, Norman F. Wyatt and Bernard Lown, Boston, Mass.*
22. External Electric Stimulation of the Heart. *Paul M. Zoll, Leona R. Norman and Arthur J. Linenthal, Boston, Mass.*
23. Chronic Anticoagulant Therapy in Recurrent Embolism of Cardiac Origin. *Stuart W. Cosgriff, New York, N. Y.*
24. The Treatment of Tuberculous Pericarditis. *Edwin M. Goyette, Edwin L. Overholt and Elliot Rapaport, Denver, Colo.*
25. Auricular Fibrillation: Circulatory Dynamics before and after Restoration of Normal Sinus Rhythm. *Ross C. Kory, Robert S. Anderson and George R. Meneely, Nashville, Tenn.*

TO BE READ IF TIME PERMITS

26. Nor-epinephrine in Shock Following Myocardial Infarction: Influence upon Survival Rate and Studies of Renal Function. *John J. Sampson and Albert Zipper, San Francisco, Cal.*
27. Total Exchangeable Sodium and Potassium in Edematous Patients. *I. S. Edelman, Laura Brooks, Graham Wilson and F. D. Moore, Boston, Mass.*

THIRD SESSION—9:00 A.M., SATURDAY, APRIL 11

Co-Chairman: Edgar V. Allen, Section on High Blood Pressure Research and Irving S. Wright, Retiring President, American Heart Association.

28. The Capillary Bed in Man and Its Functional Changes in Essential Hypertension, in Hypertension with "Cushing's Syndrome" and in Pheochromocytoma. *Richard E. Lee, New York, N. Y.*
29. An Evaluation of Vasodilator Drugs Currently Employed in the Treatment of Coronary disease. *Henry Russek, Staten Island, N. Y.*
30. Effects of Subtotal Adrenalectomy with or without Sympathectomy upon the Course of Congestive Heart Failure. *Charles C. Wolferth, William A. Jeffers, Harold A. Zintel, Joseph H. Hafkenschiel, A. Gorman Hills and Alfred M. Sellers, Philadelphia, Pa.*
31. Calcific Aortic Stenosis: Study of Blood Lipids. *Ernst P. Boas, Samuel K. Elster and David Adlersberg, New York, N. Y.*
32. The Effect of 1-Norepinephrine and Ephedrine Sulfate on Urinary Electrolyte Excretion. *Willoughby Lathem, Paul A. Marks and Betty S. Roof, New York, N. Y.*
33. The Effect of Hexamethonium upon Cerebral Circulation and Metabolism in Hypertensive Subjects before and after Surgical Sympathectomy. *Charles W. Crumpton, George G. Rowe, Robert C. Capps, Janet J. Whitmore and Quill R. Murphy, Madison, Wisc.*
34. The Effects of Progressive Anoxia on the Pulmonary Circuit in Dogs. *Carl J. Wiggers and Albert Hurlimann, Cleveland, Ohio.*
35. Panel Discussion—The Interruption of Sympathetic Pathways by Surgical and Medical Means. *John H. Talbott, Moderator*

TO BE READ IF TIME PERMITS

36. Hypertension and Coronary Occlusion. *Arthur M. Master, New York, N. Y.*
37. A Comparison of the Chylomicron Index, Serum Total Cholesterol and Lipid Phosphorus as Indices of an "Atherosclerotic State." *Willard J. Zinn and George C. Griffith, Los Angeles, Cal.*

FOURTH SESSION—2:00 P.M., SATURDAY, APRIL 11

Co-Chairmen: Nelson W. Barker and Fay A. LeFevre, Section on Circulation

38. Vascular Responses in the Kidney and Extremities to a Standard Vasodilator Stimulus after Adaptation to a Cool Environment. *Walter Redisch, Lothar Wertheimer, Claude Delislo and J. Murray Steele, New York, N. Y.*
39. Oxygen Tension of the Ischemic Limb in Various Positions. *Hugh Montgomery and Orville Horwitz, Philadelphia, Pa.*
40. George Brown Memorial Lecture—Some Chemical Factors in the Pathogenesis of Atherosclerosis. *David P. Barr, New York, N. Y.*
41. Further Considerations on the Indications for and Limitations of Direct Surgery for Arteriosclerosis. *Ormond C. Julian, William S. Dye and John Olwin, Chicago, Ill.*
42. Veratrum Treatment of Toxemia of Pregnancy: A Controlled Study. *Frank A. Finnerty, Jr. and George J. Fuchs, Washington, D. C.*
43. Studies of Vasospasm. *William T. Foley, Ellen McDevitt, John A. Tulloch and Martin Tunis, New York, N. Y.*
44. The Effects of Low-Sodium Diet and Drugs on the Digital Vascular Resistance in Hypertension. *G. H. Eurman and M. Mendlowitz, New York, N. Y.*
45. The Recognition and Treatment of Arteriosclerotic Stenosis of the Major Arteries. *Edwin J. Wylie and Joseph S. McGuiness, San Francisco, Cal.*

TO BE READ IF TIME PERMITS

46. The Control of Dicumarol Therapy in Myocardial Infarction by a Simple Blood Prothrombin Test. *Benjamin Manchester and Boris Rabkin, Washington, D. C.*
47. Familial Pheochromocytoma. *Grace M. Roth, Nicholas C. Hightower, Jr., James T. Priestley and Nelson W. Barker, Rochester, Minn.*

FIFTH SESSION—9:00 A.M., SUNDAY, APRIL 12

Co-Chairmen: George H. Humphreys II, Section on Vascular Surgery and André Cournand, Chairman, Program Committee of Scientific Council

48. The Treatment of Interauricular Septal Defects. *Robert E. Gross, Boston, Mass.*
49. The Clinical and Physiological Changes Resulting from Aortic Commissurotomy. *Charles P. Bailey, H. Goldbert, George D. Geckeler, W. Likoff and H. Bolton, Philadelphia, Pa.*
50. The Surgical Correction of Mitral Insufficiency. *Dwight E. Harken, Harrison Black, Lewis Dexter, Laurence B. Ellis and Paul Ottosen, Boston, Mass.*
51. The Surgical Treatment of Mitral Regurgitation by Elongation of the Chordae Tendineae. *F. D. Dodrill, Detroit, Mich.*
52. Cardiac Contusion from Non-penetrating Trauma to the Chest. *Arthur J. Geiger, New Haven, Conn.*
53. Mechanical and Myocardial Factors in Chronic Constrictive Pericarditis. *Rejane M. Harvey, Richard T. Cathcart and M. Irene Ferrer, New York, N. Y.*
54. Experimental and Clinical Observations on the Closure of Cardiac Septal Defects. *Harris B. Shumacker, Jr. and Harold King, Indianapolis, Ind.*
55. Panel Discussion—Surgery in Congenital Heart Disease. *Eugene C. Eppinger, Moderator*

TO BE READ IF TIME PERMITS

56. Effects of Mitral Valvuloplasty on Left Atrial Pressure Pulse Waves, with Special Reference to Mitral Regurgitation. *George N. Bedell, James W. Culbertson, Johann L. Ehrenhaft, Ernest O. Theilen and William H. Ames, Iowa City, Iowa.*
57. Results of Treatment of Hypertension by Total Sympathectomy or by Hexamethonium Orally Alone or Combined with Apresoline. *Keith S. Grimson, Edward S. Orgain, George D'Angelo and Homer A. Sieber, Durham, N. C.*

SIXTH SESSION—2:00 P.M., SUNDAY, APRIL 12

Chairman: Robert L. King, Incoming President, American Heart Association

58. Panel Discussion—The Current Status of Anticoagulant Therapy. *Edgar V. Allen, Moderator*
59. Clinical Pathological Conference. *Roy W. Scott, Moderator*

RECOMMENDATIONS FOR LABELING OF LOW SODIUM FOODS

The Association has developed recommendations to serve as guide lines for the Council on Foods and Nutrition of the American Medical Association and the Food and Drug Administration in establishing new regulations for the labeling of low sodium dietary foods.

Action was taken in this field because of the Association's interest in assuring persons on sodium-restricted diets they can depend on proper labeling of low-sodium foods and will receive what they pay for.

The recommendations prepared by a Committee of the Association under the chairmanship of Dr. Fredrick J. Stare follow:

1. Low sodium foods should be labeled with something more than the words "low sodium". They should have a statement giving the actual milligrams of sodium per unit of weight and this unit of weight might best be 3 ounces or 100 Gm. as this is a useful weight in dietetics, or a statement saying this product contains no more than x mg. per 3 ounces or 100 Gm. In addition the amount of sodium in an average serving of the product could be given—such as one slice of low sodium bread contains x mg. sodium.
2. Foods to be called low sodium foods should contain no more than the following milligrams of sodium per 100 Gm.: Meats, fish, fowl: less than 100 mg.; vegetables: less than 20 mg.; fruits, fruit juices, and fluid or reconstituted milk from dry milk substitute: less than 15 mg.; bread (low sodium): less than 10 mg.; fats, cereals: less than 5 mg. Most vegetables and meats would contain less than the amount listed, but for example carrots and liver are higher in sodium yet are permitted in many low sodium diets.
3. The responsibility for the proof of the labeling statement rests with the manufacturer. Analyses should be made of each batch of food used for the low sodium product because the same food will vary in its sodium content. An analytic check should be made at least four times a year on samples chosen at random.
4. Attention must be paid to the possible loss of other nutrients in foods treated in various ways to remove sodium. Significant loss of nutrients should be indicated on a label statement.
5. Low sodium foods should also contain a statement on the labeling to the effect that

"if low sodium foods should make up a large part of the diet for more than one month a physician should be consulted." The main purpose of such a statement is to avoid the slight possibility of a person with poor renal function receiving too great an intake of potassium.

6. Water supplies must be checked for sodium content. The public should be informed of the increase in sodium content of water softened by most chemical processes. The city or town health department should be responsible for seeing that these checks are made.
7. Trade associations of food manufacturers should be encouraged to take leadership in this field.

STATEMENT ON SCREENING AND CASEFINDING

The Association, in conjunction with the U. S. Public Health Service and the National Tuberculosis Association, has issued a statement on "The Use of 70mm Photofluorographic Films as a Method for Mass Screening for Heart Disease." The statement which resulted from a conference of these organizations called by the Association, reads:

"I. Local voluntary and official health and medical agencies should be urged to accept responsibility for setting up procedures for referral for diagnostic follow-up and supervision of those cases of suspected heart disease that are found incidentally in the course of reading mass chest x-ray survey films for tuberculosis.

"II. Facts accumulated to date do not justify, at the present time, a general recommendation to local voluntary and official agencies that any additional procedures over and above those outlined in No. I be added to mass chest x-ray screening programs in order to raise the level of case-finding for heart disease, except on a special study basis."

The statement has been distributed to health departments and tuberculosis associations as well as to affiliated heart associations.

NEW EDUCATIONAL MATERIALS

Listed below are some recent publications of interest to the physician as well as to the general public. Copies may be obtained through Heart Association affiliates, or through the National Office.

You and Your Heart, 25¢ Signet pocket edition, (paper-cover reprint) by Drs. H. M. Marvin, Irving S. Wright, Irvine H. Page, T. Duckett Jones, and David D. Rutstein. A book on the heart and circulation for the layman. For recommended reading by patients.

101 Questions About Your Child's Heart and Your Own, a comprehensive booklet answering general questions asked about cardiovascular diseases. For distribution by the physician to patients, and for use in community health-education programs.

Diagnosis of Congenital Cardiac Defects in General Practice. A handbook for the general practitioner which presents the clinical and physiologic findings and the indications for surgery in common congenital cardiac defects.

Heart Disease and Pregnancy, a booklet for young women with heart disease who plan to have children. For physicians to give their patients, and for distribution through clergymen-physician committees, prenatal clinics, and family service organizations. Complements the Children's Bureau publication, Prenatal Care.

Your Heart and How It Works, Heart Diagram with descriptive caption on $8\frac{1}{2}$ x 11 sheet. Suitable for use in study groups, clinics, schools and lectures.

Complete list of available materials may be obtained from Heart Associations.

MEETINGS

Apr. 8–12: Twenty-Ninth Annual Meeting, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 8–9: Assembly panels, Assembly meeting, meeting of the Scientific Council, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 9–12: Twenty-Sixth Scientific Sessions, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 13–17: American College of Physicians, 34th Annual Meeting, Hotel Haddon Hall–Chalfonte, Atlantic City, N. J.

Apr. 20–22: Areal Meeting, American Academy of Pediatrics, Hotel Statler, Boston, Mass. Executive Secretary, E. H. Christopherson, M.D., American Academy of Pediatrics, 610 Church Street, Evanston, Ill.

Apr. 23–25: 1st Western Hemisphere Conference of World Medical Association, Richmond, Va. Secretary-General, Dr. Louis H. Bauer, World Medical Association, 2 East 103rd Street, New York 29.

May 3: National Meeting, American Federation for Clinical Research, Steel Pier, Atlantic City, N. J. Convention headquarters at Haddon Hall Hotel. National Secretary, Dr. Lawrence E. Hinkle, Jr., M.D., 525 E. 68th St., Room F-611, New York 21, N. Y.

May 7–10: National Congress of Cardiology, Sevilla, Spain. Secretary, Dr. E. Benot, 3 Paseo de las Delicias, Sevilla, Spain.

May 15–16: Annual Meeting, Council for High Blood Pressure Research, Cleveland, Ohio. George Wakerlin, M.D., Chicago, Cli. Prog. Com., 1853 W. Polk St., Chicago 12, Ill.

May 28–31: 19th Annual Meeting, American College of Chest Surgeons, Hotel New Yorker, New York City. Executive Director, Murray Kornfeld, American College of Chest Surgeons, 112 East Chestnut Street, Chicago 11, Ill.

June 1–5: Annual session, American Medical Association, New York City. Secretary, Dr. George F. Lull, 535 N. Dearborn Street, Chicago 10, Ill.

June 7–9: American College of Cardiology, second annual Convention, Hotel Statler, Washington, D.C. Secretary, Philip Reichert, M.D., 480 Park Avenue, New York 22, N. Y.